Revascularization Saves Lives of Heart Attack Patients Experiencing Cardiogenic Shock

Background: Medical advances have enabled many heart attack survivors to live longer with improved quality of life. However, the benefits to patients whose heart attacks are complicated by acute heart failure have been limited. The leading cause of death for these patients is cardiogenic shock (a form of shock that occurs when the heart loses its ability to supply enough blood to the body), which develops in the days following a heart attack. The initially damaged heart becomes progressively weaker because its impaired pumping ability exacerbates the damage by diminishing its supply of oxygenated blood.

Advance: The SHOCK Trial evaluated whether restoring blood flow to the heart via a revascularization procedure can save the lives of patients who develop cardiogenic shock. It revealed that patients who receive revascularization immediately after developing cardiogenic shock are significantly more likely to be alive one year after their heart attacks than are those who do not. However, revascularization did not seem to help heart attack patients in cardiogenic shock if they were 75 years old or older.

Implications: Based on these results, the American College of Cardiology and the American Heart Association now recommend prompt revascularization for patients younger than 75 years who develop cardiogenic shock within 36 hours of a heart attack.

Hochman JS, Sleeper LA, White HD, Dzavik V, Wong SC, Menon V, Webb JG, Steingart R, Picard MH, Menegus MA, Boland J, Sanborn T, Buller CE, Modur S, Forman R, Desvigne-Nickens P, Jacobs AK, Slater JN, and LeJemtel TH: One-year survival following early revascularization for cardiogenic shock. The Journal of the American Medical Association 285: 190-192, 2001.

Gene Therapy May Save Diabetic Patients' Legs

Background: Diabetes, especially non-insulin dependent diabetes mellitus (type 2 diabetes), has become a major public health issue. A significant percentage of hospital admissions attributed to diabetes are due to conditions affecting patients' legs. Many are caused by a loss of sensation due to nerve damage, which leads to irremediable ulcers that may ultimately necessitate amputation of the affected limb. Heretofore, no one knew what caused this damage, but some hypothesized that the nerves were being destroyed because of damage to the tiny blood vessels that nourish them.

Advance: Researchers studying animal models of diabetes have confirmed that both type 1 and type 2 diabetes destroy blood vessels that nourish nerves in the legs and feet. Moreover, they were able to restore the blood vessels and reverse the nerve damage by injecting the gene for vascular endothelial growth factor (VEGF) into the animals' affected limbs.

The researchers, concerned that VEGF may also cause blood vessel growth that could damage the kidneys, monitored the animals' renal function and performed histological analysis of the kidneys. They did not detect any damage, which was consistent with results from studies of VEGF gene therapy in patients with other vascular conditions

Implications: At this time, no effective treatment exists for diabetes-related leg diseases. If VEGF gene transfer can restore nerve and limb function and is shown to be safe in humans, it could prevent many of the 86,000 diabetes-related amputations that are performed annually. In addition to decreasing diabetes-associated morbidity, it would likely reduce prolonged, recurrent, extensive hospitalizations and their associated costs.

Schratzberger P, Walter DH, Rittig K, Bahlmann FH, Pola R, Curry C, Silver M, Krainin JG, Weinberg DH, Ropper AH, and Isner JM: Reversal of experimental diabetic neuropathy by VEGF gene transfer. Journal of Clinical Investigation 107: 1083-1092, 2001.

Beta-Blocker Does Not Increase Survival of Black Patients with Advanced Heart Failure

Background: Heart failure is the most common reason for hospitalization in the elderly and is increasing in prevalence. A class of drugs commonly referred to as beta-blockers reduces morbidity and mortality in patients with mild-to-moderate heart failure, but their effects in patients with more advanced disease are unclear. To test the effect of beta-blockers on survival in patients with moderate-to-advanced stages of heart failure, Beta-Blocker Evaluation of Survival Trial (BEST) investigators compared the effects of bucindolol, a beta-blocker selected because the doses at which it is safe for people with severe heart failure are known, with those of a placebo.

Advance: The BEST showed that, overall, bucindolol did not increase survival for patients with moderate to severe heart failure. Consistent with results from other studies of beta-blockers, however, bucindolol conveyed some benefit (compared to the placebo) to patients with less advanced disease. Surprisingly, subgroup analysis indicated that the effects of bucindolol also varied with race; black heart failure patients received no benefit from bucindolol, while non-black patients (whites, Hispanics, Asian/Pacific Islanders, and American Indian/Alaskan Natives) treated with the drug lived longer.

Implications: In addition to underscoring the importance of examining gender, racial, and ethnic differences in future studies of cardiovascular disease, the results demonstrate the importance of treating heart failure early, when beta-blockers can make a real difference in survival. In an NIH press release, BEST Co-Chair Dr. Eric Eichhorn of the Dallas VA Medical Center stated, "Based on the large amount of evidence of benefit of beta-blockers from previous studies, beta-blockers should be considered for all heart failure patients at this time, including African-American patients." However, more research is needed to understand which patients will benefit from which of the numerous beta-blockers available.

The Beta-Blocker Evaluation of Survival Trial Investigators: A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. The New England Journal of Medicine 344: 1659-1667, 2001.

Inhaled Corticosteroids are Safe and Effective for Children with Asthma

Background: The use of corticosteroids as treatment for children with asthma has been a subject of concern among pediatricians and parents alike. The advent of inhaled corticosteroids promised reduced risk of side effects seen with oral corticosteroids because less medication would be absorbed into the blood stream. Even so, there has been a lingering reluctance among physicians to prescribe, and among parents to allow their children to use, inhaled corticosteroids.

Advance: Researchers in the Childhood Asthma Management Program (CAMP) recently studied over one thousand 5 to 12 year old children with mild-to-moderate asthma to compare daily inhaled corticosteroid (budesonide) therapy with daily inhaled noncorticosteroidal anti-inflammatory (nedocromil) therapy and with a placebo. Neither drug improved lung function in the children. However, budesonide provided better asthma control than either nedocromil or placebo, as reflected in fewer emergency room visits, hospitalizations, and days when asthma episodes were experienced. Moreover, it was safe. Although children treated with budesonide experienced, on average, a slight lag in growth (height) in the first year of treatment as compared to other children in the CAMP, they grew at the same rate as others during the remaining four years of the study.

Implications: Results of the CAMP should alleviate concerns about efficacy and safety expressed by primary care physicians and parents alike. The findings demonstrate the benefit of using inhaled corticosteroids to treat children with asthma. The drug not only has medical benefits, but also has social, developmental, and educational implications for children with asthma – with their disease "under control," children can participate more fully in childhood activities.

Childhood Asthma Management Program Research Group: Long-term effects of budesonide or nedocromil in children with asthma. The New England Journal of Medicine 343: 1054-1063, 2001.

Inhaled Corticosteroids Do Not Slow Progression of COPD

Background: Chronic obstructive pulmonary disease (COPD) is a progressive disease, usually related to cigarette smoking, that affects 15 million Americans and is the fourth leading cause of death in this country. Since attempts to reduce rates of smoking have had limited success, COPD will likely continue to be a major cause of disability and premature death for many years to come. Improvements are needed in our understanding of the disease process and in our methods for treating patients with this disease. Currently, COPD patients are treated with inhaled corticosteroids for symptomatic relief; these drugs also were thought to slow the decline in lung function that makes COPD ultimately fatal.

Advance: A randomized, placebo-controlled clinical trial showed that treatment with inhaled corticosteroids did not slow progression of COPD. However, the patients taking corticosteroids had fewer symptoms, lower health-care utilization, and some decrease in the sensitivity of the lungs to external stimuli compared with members of the placebo group. Bone loss was a significant side effect in corticosteroid users.

Implications: This study shows that the role of inhaled corticosteroids in COPD should be to reduce symptoms rather than to modify the course of the disease, and any benefit should be weighed against the potential long-term side effects.

Lung Health Study Research Group: Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. The New England Journal of Medicine 343: 1902-1909, 2000.

Arginine Supplements May Benefit Patients with Sickle Cell Disease

Background: Adults with sickle cell disease (SCD) are deficient in the amino acid L-arginine (L-Arg). One of the body's uses for L-Arg is to make nitric oxide (NO), a compound with numerous biological roles. For example, NO is involved in dilating blood vessels and preventing blood cells from adhering to one another as they do in the painful vaso-occulsive crises (VOC) that make SCD so devastating.

In addition to having low blood levels of L-Arg, sickle cell patients hospitalized for VOC have diminished levels of NO byproducts formed as the body uses NO. Moreover, there appears to be an inverse relationship between the amount of pain reported by SCD patients experiencing VOC and their blood levels of NO byproducts, indicating an association between impaired NO metabolism and vaso-occulsion. Therefore, researchers at the Northern California Comprehensive Sickle Cell Center speculated that giving patients L-Arg supplements would ease the pain associated with VOC by increasing the amount of NO available to be metabolized.

Advance: This is the first study to report the effects of L-Arg supplementation on NO production and metabolism in SCD patients. The researchers report SCD patients metabolize L-Arg and NO faster than normal controls; the production and breakdown of NO is accelerated even further during VOC. Because administering L-Arg supplements during VOC appears to accelerate NO metabolism in a dose-dependent manner (i.e., the more L-Arg given, the more NO produced and used), the authors conclude that the availability of L-Arg may be the rate-limiting step in nitric oxide metabolism during VOC.

Implications: Giving L-Arg supplements to SCD patients during VOC appears to increase NO production and, consequently, its metabolism. Other studies have demonstrated that L-Arg is safer and more easily administered than inhaled NO. Therefore, if L-Arg therapy is successful in a large number of SCD patients, it will be a valuable treatment option for severely ill SCD patients.

Morris CR, Kuypers FA, Larkin S, Sweeters N, Simon J, Vichinsky EP, and Styles LA: Arginine therapy: a novel strategy to induce nitric oxide production in sickle cell disease. British Journal of Haematology 111: 498-500, 2000.

New, Low Cost Immunosuppressive Therapy for Aplastic Anemia is Deemed to be "Dangerous"

Background: Patients with severe aplastic anemia (SAA) traditionally receive immunosuppressive therapy regimens containing antithymocyte globulin (ATG). However, approximately one-third of them relapse, and others develop additional blood disorders that are difficult to treat. Therefore, when 10 SAA patients went into remission following treatment with another immunosuppressive agent, cyclophosphamide, without any incidence of relapse and or other complications associated with ATG therapy, cyclophosphamide was embraced as a potential cure. It became particularly popular in developing countries because it is less expensive than ATG.

Advance: A randomized clinical trial to compare the ATG- and cyclophosphamide-based treatments was stopped early because of unexpectedly high mortality associated with the cyclophosphamide therapy. In the peer-reviewed journal article announcing their results, the researchers stated "cyclophosphamide seems a dangerous choice for treatment of [SAA], given the good results achievable with standard therapy."

Implications: The study provides scientific evidence needed to resolve whether ATG or cyclophosphamide is the better treatment for SAA patients. The results also validate anecdotal reports made by physicians in less affluent countries who observed that SAA patients experienced higher mortality after cyclophosphamide therapy replaced the ATG regime. Moreover, the study illustrates the importance of well-designed clinical trials in determining safe and effective therapies.

Tisdale JF, Dunn DE, Geller N, Plante M, Nunez O, Dunbar CE, Barrett AJ, Walsh TJ, Rosenfeld SJ, and Young NS: High-dose cyclophosphamide in severe aplastic anaemia: a randomised trial. The Lancet 356: 1554-1559, 2000.

Gene Therapy and Aminoglycoside Protection

Background: Aminoglycosides are a class of antibiotics sometimes prescribed for a variety of severe infections. Unfortunately, aminoglycoside treatment can cause degeneration of inner ear hair cells and hearing loss, which is called aminoglycoside ototoxicity. At present, there is no clinical treatment for the irreversible ototoxic effects of aminoglycosides. One potentially promising treatment to prevent or reverse this ototoxicity involves gene therapy. However, efficient delivery and expression of a desired gene are critical to the success of gene therapy, and delivery to the inner ear can be especially difficult.

Advance: NIH-supported investigators are currently working to elucidate many of the cellular and molecular mechanisms important for inner ear gene delivery. One such study has demonstrated significant protective levels against ototoxic damage following the delivery of the gene encoding glial cell line-derived neurotrophic factor (GDNF), a protein that affects the development and survival of neurons in the central and peripheral nervous system. Using viruses to carry the gene encoding GDNF, NIH-supported investigators demonstrated the successful delivery and expression of GDNF in the inner ear and subsequent preservation of hearing upon exposure to aminoglycosides in a mouse model system. While using viruses to deliver genes has been successful, NIH-supported investigators are exploring other avenues of gene delivery systems to the inner ear, including the use of a gelatin sponge for delivery. In this case, the desired gene is soaked into the sponge and directly placed on the round window membrane opening of the inner ear. Investigators showed expression and presence of the targeted gene throughout the inner ear. This type of delivery system could allow a more direct and less laborious delivery process.

Implications: These multifaceted research approaches to gene delivery hold promise for future treatment of sensory hearing loss and enhanced quality of life for affected individuals.

Jero J, Mhatre AN, Tseng CJ, Stern RE, Coling DE, Goldstein JA, Hong K, Zheng WW, Hoque ATMS, and Lalwani AK: Cochlear gene delivery through an intact round window membrane in mouse. Human Gene Therapy 12: 539-548, 2001.

Complete Remission and Preservation of Voice and Speech in Patients with Head and Neck Cancer Using Chemotherapy and Radiation

Background: Over 300,000 Americans suffer partial or complete loss of voice and speech as a result of cancer of the head and neck, and 12,000 of these patients die each year. NIH intramural scientists have collaborated to develop new therapy alternatives to surgery for patients with head and neck cancer which result in remission and preservation of the organs involved in voice and speech.

Advance: NIH scientists completed a phase I clinical trial to determine the tolerance and response of patients with advanced head and neck cancer to combined treatment with the chemotherapy agent Paclitaxel (taxol) and radiation. The study was based on the laboratory observation that taxol can sensitize and increase response of cancer cells to radiation. All of the patients entering the study had advanced or inoperable cancer of the head and neck. Seventy percent of patients with advanced cancers attained a complete remission, and preservation of voice and speech. Fifty one percent remain in complete remission and 56 percent are alive 3 years after treatment, which is similar or better than results obtained with surgery in patients at the same stage. Treatment as an outpatient was well tolerated due to a low incidence of acute toxicity from chemotherapy, but side effects of the combined therapy included a delay of several months in recovery of swallowing, which was relieved by nutritional supplements.

Implications: Future studies are likely to include addition of a drug to reduce the side effects experienced in this trial, and addition of new drugs that target the specific molecular abnormalities that cause cancers involving the vocal tract.

Sunwoo JB, Herscher LL, Kroog GS, Thomas GR, Ondrey FG, Duffey DC, Solomon BI, Boss C, Albert PS, McCullugh L, Rudy S, Muir C, Zhai S, Figg WD, Cook JA, Mthchell JB, and Van Waes C: Concurrent paclitaxel and radiation in the treatment of locally advanced head and neck cancer. Journal of Clinical Oncology 19: 800-811, 2001.

Clinical Trial Underway for a New Drug for Treatment of Patients with Vocal Tract (Head And Neck) Cancer

Background: Over 300,000 Americans suffer from cancer of the head and neck, and 12,000 of these patients die each year.

Advance: NIH scientists have identified a new target for therapy of cancers of the vocal tract (head and neck) and will conduct a Phase I trial of a new drug to be given in combination with radiation for treatment of patients with cancers of the vocal tract (head and neck). NIH investigators showed that an investigational agent, PS-341, blocks activation of a pathway that is necessary for head and neck cancer cells to grow and to form blood vessels that promote tumor growth. They showed that a signal called Nuclear Factor kappaB is permanently switched on in head and neck cancers, and activates other genes that cause these cancers to grow. They also showed that blocking activation of Nuclear Factor kappaB with PS-341 inhibited survival and growth of cancer cells from patients, when the cells were grown either in the laboratory or in mice. These studies were supported by a Cooperative Research and Development Agreement between the NIH and Millennium Pharmaceuticals, the company that produces PS-341. The clinical trial is expected to take two years.

Implications: Studies to identify the genes activated by Nuclear factor kappaB which cause these cancers are also underway, so that new tests may be developed for diagnosis and selection of the best therapy for patients.

Sunwoo JB, Chen Z, Dong G, Yeh N, Bancroft CC, Sausville E, Adams J, Elliott P, and VanWaes C: Novel proteasome inhibitor PS-341 inhibits activation of nuclear factor-κB, cell survival, tumor growth and angiogenesis in squamous cell carcinoma. Clinical Cancer Research 7: 1419-1428, 2001.

Prevalence of Otitis Media in Childhood and Treatment

Background: There have been scant data available to examine the incidence and/or prevalence of ear tube insertions in young children in the U.S.

Advances: In a recent study, four nationally representative surveys conducted annually by the National Center for Health Statistics were used to derive estimates for the prevalence of otitis media (OM) diagnosis based on physicians' office, emergency room, and hospital records. Of all ambulatory care visits in 1996, almost half (45 percent) were for children in the first 2 years of life. Also, 60 percent of OM visits were for children in the first 3 years of life. Boys had a 12.5 percent higher rate of visits for OM. Hispanic children less than 6 years of age were diagnosed with OM more often than white children and significantly more often than black children. In comparing the principal diagnosis to all diagnoses of OM for children less than 6 years, we found that 78 percent were the principal diagnosis in 1996. Unlike the time period from 1975 to 1990, for which a steadily increasing rate of OM diagnoses has been reported, in the recent period from 1990 to 1996, the OM diagnosis rate in the U.S. has leveled off. Estimates of myringotomy with tube insertion (MT) declined from 1994 to 1996 (101.1 to 88.6 per 10,000 children). A total of 512,000 MT were performed in children less than 15 years old, of which 416,000 (81 percent) were in children less than 6 years old. Ninety-seven percent of these procedures were performed on outpatients.

Implications: Monitoring national trends in OM diagnosis and treatment will provide a valuable tool for assessing progress in OM prevention in the future, thereby enabling careful evaluation of new treatments such as vaccines that are beginning to be extensively tested against the common bacterial pathogens and viral progenitors of OM.

Nalluswami K, Hildesheim ME, and Hoffman HJ: Prevalence estimates of physicians' office, emergency room, and hospital visits for otitis media treatments, United States, 1996. Proceedings of the Seventh International Symposium: Recent Advances in Otitis Media. Hamilton, Ontario: BC Decker, Inc. (in press).

Working to Cure Prion Diseases

Background: Prion diseases are a group of fatal neurodegenerative disorders that occur in humans and animals. Prions are infectious proteins that alter the shape of a normal cellular protein, changing it into a prion. Prions accumulate in the nervous system and produce an invariably fatal and currently untreatable neurological disease characterized by sponge-like holes in the brain. The human forms of these diseases, including Creutzfeld-Jakob disease (CJD), are relatively rare. Animal prion diseases include scrapie in sheep and bovine spongiform encephalopathy (BSE) in cows. Of recent concern is the recent epidemic of BSE, or "mad cow disease," in Great Britain and parts of Western Europe, and its apparent transmission to humans through consumption of infected meat producing a new variant of CJD (nvCJD). The 100th human death attributable to this disease occurred in England in May.

Advance: Prions from BSE-infected cells were totally destroyed by low concentrations of branched polyamines (large molecules with many amino group branches). However, the structure of these polyamines limits their ability to cross the blood-brain barrier and hence they cannot gain access to and destroy prions in brain. Another approach to development of drugs to treat the prion diseases comes from using computer-based models of prion structure to determine how best to interfere with their formation. Using this strategy, over 200,000 potential compounds were screened and four were found to be effective in clearing prions from cells in tissue culture. Other screening approaches of drugs known to enter the brain resulted in the finding that quinacrine (an anti-malarial drug) and chlorpromazine (an anti-psychotic drug) also caused the clearance of prions from cells in tissue culture. Since these compounds were effective at non-toxic concentrations and have been used for many years in humans, it is possible to start initial clinical trials to test their efficacy in treating persons with CJD who otherwise face certain death.

Implications: The potential threat of a larger epidemic of nvCJD mandates an increased effort to find therapeutic agents that will cure prion diseases. These recent papers present some approaches and new leads for the treatment and possible prevention of these fatal neurodegenerative disorders.

Korth C, May BCH, Cohen FE, and Prusiner SB: Acridine and phenothiazine derivatives as pharmacotherapeutics for prion disease. Proceedings of the National Academy of Sciences USA 98: 9836-9841, 2001.

Perrier V, Wallace AC, Kaneko K, Safar J, Prusiner SB, and Cohen FE: Mimicking dominant negative inhibition of prion replication through structure-based drug design. Proceedings of the National Academy of Sciences USA 97: 6073-6078, 2000.

Supattapone S, Wille H, Uyechi L, Safar J, Tremblay P, Szoka FC, Cohen FE, Prusiner SB, and Scott MR: Branched polyamines cure prion-infected neuroblastoma cells. Journal of Virology 75: 3453-3461, 2001.

Low-dose Estrogen Reduces Bone Breakdown in Older Women

Background: Estrogens have been shown to diminish bone loss (osteoporosis) in women. However, many older women are reluctant to take estrogens for prevention of osteoporosis because of side effects. These include breast tenderness, bloating, fluid retention, headache, and vaginal bleeding. Many older women and their doctors also have concerns about uncertainty regarding estrogen's effects on risks for age-related conditions such as breast cancer and coronary heart disease. Since the risk of adverse effects of a treatment is usually related to the dose taken, the lowest dose needed to produce a desired effect (in this case preventing osteoporosis) is preferred. Thus, it is important to determine if lower doses of estrogens than are currently used provide satisfactory protection against bone loss in women.

Advance: More than 100 black, Hispanic, and white women over the age of 65 participated in a study of three different doses of estrogen (17 estradiol) therapy. The highest of these doses, is the amount most commonly used today in estrogen replacement therapy, and the lowest dose was one-fourth of this amount. The participants were studied for six months: three months on treatment and three months off. The low dose markedly reduced bone breakdown as measured by several serum markers. This reduction was similar to that produced by the highest estrogen dose. Breast tenderness, bleeding, and thickening of the lining of the uterus (an indicator of potential adverse uterine effects), were significantly less frequent with the lowest dose. In fact, low dose therapy resulted in no more side effects than placebo.

Implications: This study indicates that low-dose estrogen therapy may be an effective, safer, and more tolerable intervention for osteoporosis prevention in older women compared to the commonly prescribed higher-dose therapy. With fewer undesirable side effects, low-dose therapy could not only provide an alternative for older women currently taking estrogens, but also could provide an acceptable treatment for those who would otherwise decline to take estrogens or discontinue treatment because of adverse side effects. Long-term studies are needed to determine whether the effects on bone metabolism seen with low dose estrogens will translate into increases in bone density and decreased incidence of fractures.

Prestwood KM, Kenny AM, Unson C, and Kulldorff M: The effect of low dose micronized 17B estradiol on bone turnover, sex hormone levels, and side effects in older women: a randomized, double blind, placebo-controlled study. Journal of Clinical Endocrinology Metabolism 85: 4462-4469, 2000.

Potential New Treatment for Type 2 Diabetes Mellitus in the Elderly

Background: Type 2 diabetes mellitus (DM) is the most common form of diabetes in the elderly population. It is caused by an inability of the beta cells of the pancreas to keep up with increasing insulin demands; consequently, blood glucose levels rise. Present treatments for type 2 DM are less than adequate. Scientists are searching for compounds that will maintain insulin production by pancreatic beta cells to prevent the progressive rise in blood glucose that occurs in type 2 DM. GLP-1, a gut peptide, can stimulate beta cells to produce more insulin in middle aged persons with type 2 DM, but had not been tested in older adults who make up the majority of patients with type 2 DM. In addition, the biologic half-life of GLP-1 is short, and its effects quickly wear off, leading researchers to attempt to synthesize related compounds that will be effective over a longer period of time.

Advances: Promising studies in rodents and in middle-aged humans led researchers to study how effective GLP-1 would be in elderly patients. Studies showed that GLP-1 potently stimulated insulin release in the elderly and lowered blood glucose to normal levels. In parallel studies with old rodents, investigators found that when GLP-1 was given long-term, it increased the number and activity of pancreatic beta cells. In efforts to synthesize a longer-acting form of GLP-1, researchers modified regions of the peptide that are susceptible to degradation, producing a molecule that maintained its biological activity over an extended time.

Implications: These results have major implications for the use of a GLP-1-type agent in the treatment of type 2 DM. Progressive beta cell failure is a characteristic of type 2 DM that is not modified by available treatment regimens. Animal studies strongly suggest that GLP-1 can augment the number and function of beta cells. The encouraging results in short term studies of elderly humans have led to an ongoing trial of longer term GLP-1 treatment. Of practical importance for eventual routine treatment of patients with type 2 DM, long-acting forms of GLP-1 are being developed.

Meneilly GS, McIntosh CHS, Pederson RA, Habener JF, Gingerich R, Egan JM,and Elahi DE: Glucagon-like peptide-1 (7-37) augments insulin release in elderly patients with diabetes. Diabetes Care 964-965, 2001.

Perfetti R, Zhou J, Doyle ME, and Egan JM: GLP-1 induces cell proliferation, PDH-1 expression and increases endocrine cell mass in the pancreas of old, glucose-intolerant rats. Endocrinology 141: 4600-4605, 2000.

Doyle ME, Greig NH, Holloway HW, Betkey, JA, Bernier M, and Egan JM: Insertion of an N-terminal norleucine after the 7-amino acid position of glucagon-like peptide-1 produces a long acting hypoglycemic agent. Endocrinology 142: (in press 2001).

Copper/Zinc Chelator Reduces Amyloid Accumulation in Transgenic Mice

Background: Earlier work has indicated that copper (Cu) and zinc (Zn) are concentrated in the amyloid plaques found in the brains of Alzheimer's disease (AD) patients. Although controversial, some believe that the amyloid-beta (A) peptide that makes up these plaques possesses binding sites for Cu and Zn that are responsible for its resistance to breakdown by enzymes, its tendency to aggregate, and its toxicity. In the test tube, compounds that can chelate, or bind, both Zn and Cu can cause A deposits from the brains of AD patients to go into solution. The next step was to determine if such an approach could successfully be used in an animal model of AD.

Advance: Mice developed as a transgenic model of AD were treated with clioquinol (CQ), an antibiotic that can cross into the brain from the blood and bind to Cu and Zn. Following treatment of 12 month old transgenic mice with CQ for 12 weeks, there was a significant reduction in plaque surface area and a 65 percent decrease in A peptide in brain. Of note, two of the six animals treated with CQ had no A peptide and no detectable amyloid pathology. Twenty older transgenic mice (21 months of age) treated at a higher dose for just 9 weeks were also examined. After treatment, there was a 49 percent reduction in brain A. CQ did not decrease levels of the amyloid precursor protein, the precursor of A, nor of a neuronal protein involved in neuron-neuron communication, suggesting that it was not toxic to brain.

Implications: This is an innovative approach for eliminating amyloid deposits in a transgenic mouse model of AD. The success of the therapy implies that removing metal ions by chelation can solubilize amyloid peptide, allowing its degradation or removal from brain. The results suggest that the drug may be a suitable candidate for clinical trials with AD patients.

Cherny RA, Atwood CS, Xilinas ME, Gray DN, Jones WD, McLean CA, Barnham KJ, Volitakis I, Fraser FW, Kim YS, Huang X, Goldstein LE, Moir RD, Lim JT, Beyreuther K, Zheng H, Tanzi RE, Masters CL, and Bush AI: Treatment with a copper-zinc chelator markedly and rapidly inhibits beta-amyloid accumulation in Alzheimer's disease transgenic mice. Neuron 30: 665-676, 2001.

Melatonin Helps Some Older Insomniacs Sleep Better

Background: It has been estimated that insomnia affects about a third of the older population in this country. This inability to have restful sleep at night results in excessive daytime sleepiness, attention and memory problems, depressed mood, and lowered quality of life. Treatments of sleep problems often are limited to hypnotic medications that have potential adverse effects and bring only temporary relief of insomnia rather than correcting the underlying sleep processes. Melatonin is a hormone produced by the pineal gland, which signals the brain about the onset of night and cues the brain that it is time to sleep. Primarily as the result of several popularized books, melatonin has become available over the counter as a dietary supplement, presented as a natural hormone that can improve sleep. Data now are available indicating that low doses of melatonin may be effective in improving the quality of sleep in some older insomniacs.

Advance: A double blind, placebo-controlled clinical trial of melatonin was conducted on individuals age 50 and older with and without insomnia. Self-reports of insomnia were confirmed by measurements of body movements through the night period at home as well as by measurements of brain activity, movements, and breathing during sleep in the sleep laboratory. Each participant received placebo or different doses of melatonin (0.1, 0.3, and 3.0 mg) orally one-half hour before usual bedtime for one week in a random order, each followed by a one-week washout period. The highest dose (3.0 mg) is the dose commonly found in over-the-counter preparations and results in blood levels 10 to 20 times the normal physiological levels produced by the lower doses. The most effective dose for improving the quality of sleep, measured as sleep efficiency or the proportion of time in bed actually sleeping, was 0.3 mg. The highest dose, like the lowest dose, also improved sleep efficiency, although to a lesser extent. However, the 3 mg dose also significantly reduced nighttime body temperature and increased daytime melatonin levels. There was no relation found between a subject's own endogenous melatonin levels and sleep efficiency. Individuals with normal sleep were unaffected by any dose of melatonin.

Implications: The results of this study demonstrate that low doses of melatonin that raise blood levels to the normal nighttime range can significantly improve the quality of sleep in older people suffering from age-related insomnia over a one-week treatment period. The treatment did not affect sleep of older people in whom sleep is normal.

Zhdanova IV, Wurtman RJ, Regen MM, Taylor JA, Shi JP, and Leclair OU: Melatonin treatment for age-related insomnia. Journal Clinical Endocrinology Metabolism (in press 2001).

Old Drugs Learn New Tricks

Background: Diseases caused by tropical parasites are a major worldwide health problem. According to the World Health Organization, malaria alone kills more than 1 million people per year across the globe, and a child dies of malaria every 30 seconds. Other scourges caused by parasites include Chagas' disease, leishmaniasis, sleeping sickness, and the AIDS-related infections toxoplasmosis and cryptosporidiosis. Scientists have not yet succeeded in developing vaccines against these parasitic infections, which collectively affect 3 billion people worldwide. As a result, there is an urgent need for new, inexpensive treatments for these diseases.

Advance: A team of chemists has discovered that a class of drugs called "bisphosphonates," which are currently approved by the Food and Drug Administration to treat osteoporosis and other bone ailments, may also be useful for treating malaria, Chagas' disease, leishmaniasis, and the AIDS-related infections. Previous studies by the researchers had hinted that the active ingredient in medicines such as Fosamax^{Ô}, Actonel^{Ô}, and Aredia^{Ô} blocks a key step in parasite metabolism. To test whether this was true, the researchers gave the medicines to five different parasites, each cultured in a plastic lab dish. The scientists found that low concentrations of the osteoporosis drugs killed the parasites, while sparing human cells. The researchers are now testing the drugs in animal models of the parasitic diseases and so far have obtained cures – in mice – of certain types of leishmaniasis.

Implications: Patients and doctors alike benefit when existing drugs find new uses. Especially since research efforts to develop vaccines against parasites have been largely unsuccessful to date, there is an urgent need for scientists to come up with new medicines to attack tropical parasites, which have also begun to develop resistance to currently effective anti-microbial medicines. If the ongoing studies demonstrate that bisphosphonate drugs work in larger animal models, the next step will be to determine if the medicines can thwart parasitic infections in humans. This process could occur relatively quickly, since the medicines have already been approved for other uses, and therefore have already been tested for safety in people.

Martin MB, Grimley JS, Lewis JC, Heath HT, Bailey BN, Kendrick H, Yardley V, Caldera A, Lira R, Urbina JA, Moreno SNJ, Docampo R, Croft SL, and Oldfield E: Bisphosphonates inhibit the growth of *Trypanosoma brucei*, *Trypanosoma falciparum*: a potential route to chemotherapy. Journal of Medical Chemistry 44: 909-916, 2001.

Tiny Nanotubes as New Antibiotics

Background: One of medicine's greatest triumphs – the development of antibiotics – is steadily growing into one of medicine's greatest fears: that the infectious diseases easily vanquished decades ago will be as deadly to our grandchildren as they were to our grandparents. Within recent years, for example, hospital workers in the U.S. have detected strains of Staphylococcus aureus – "staph," the leading cause of hospital-acquired infections – that are resistant to every known antibiotic medicine. The race is on to find new types of antibiotic medicines.

Advance: Chemistry to the rescue! Scientists have now devised a clever chemical scheme to create a novel class of antibiotic compounds. A team of researchers invented a way to get laboratory-made rings and strings of amino acids (peptides) to assemble themselves into channels and pores. With just the right mix of ingredients and conditions, the researchers coaxed the rings to stack on top of each other, forming a tube. The artificial tubes work as antibiotics by poking holes in bacterial membranes, making them too leaky to hold their contents. The research team found that the tiny tubes kill a variety of bacteria in laboratory experiments. The scientists went on to test the compounds in mice infected with a lethal dose of drug-resistant bacteria and discovered that all of the mice survived over the course of a 7-day study. In contrast, all the mice in the control group (receiving no nanotubes) died within 48 hours.

Implications: This new work holds great promise that a new class of nanotube peptides can be effective in treating potentially fatal antibiotic-resistant infections caused by staph and other dangerous microbes.

Fernandez-Lopez S, Kim HS, Choi EC, Delgado M, Granja JR, Khasanov A, Kraehenbuehl K, Long G, Weinberger DA, Wilcoxen K, and Ghadiri MR: Antibacterial agents based on the cyclic D, L-alpha-peptide architecture. Nature 412**:** 452-455, 2001.

Ganz, T: Chemistry: rings of destruction. Nature 412: 392-933, 2001.

Reversal of Diet-induced Insulin Resistance: Another Use for Aspirin?

Background: Diabetes is a chronic disease characterized either by an inability to produce insulin (type 1 diabetes) or by the body's inability to use its own insulin (type 2 diabetes) to regulate blood levels of the sugar, glucose. It is the seventh leading killer in this country with costs in excess of $98 billion each year. Insulin resistance can be defined as a cluster of abnormalities, including obesity, hypertension, abnormal lipid levels and type 2 diabetes, that are associated with insulin resistance and compensatory excessive production of insulin. The syndrome is characterized by diminished cellular and metabolic responses to the actions of insulin. To compensate for resistance, the pancreas secretes more insulin causing high circulating plasma insulin levels. The causes of insulin resistance and likewise the mechanisms by which weight loss and exercise reverse its effects are largely unknown.

Aspirin is one of the salicylate class of chemicals that might provide a clue to treatment of insulin resistance. Salicylates are anti-inflammatory compounds that interrupt the cascade of molecular events that lead to inflammation. High doses of aspirin and other salicylate-containing drugs are used to treat rheumatic fever, rheumatoid arthritis and other inflammatory diseases. High doses of salicylates also decrease blood sugar but their potential for treatment of diabetes has largely been forgotten. Classically, aspirin has been believed to exhibit anti-inflammatory actions due to the inhibition of cyclooxygenases (COX), enzymes that are important in the inflammatory pathway. Results reported here suggest that another enzyme in the inflammatory cascade, IκB kinase β (IKKβ), rather than COX is the molecular target of salicylates. IKKβ activates NfκB which is a major regulator of immune responses stimulated by pro-inflammatory stimuli such as tumor necrosis factor (TNFα). NIH-supported scientists investigated the possible involvement of the IKKβ complex in insulin resistance and aspirin as a possible treatment.

Advance: In severely insulin-resistant laboratory rats and mice, high doses of aspirin or sodium salicylate (equivalent to a 150 pound person taking 25 aspirin tablets per day) reversed the high blood sugar and insulin levels. Additional experiments using cell cultures showed that TNFα, which activates the IKKβ complex, induced insulin resistance. However, the COX inhibitors ibuprofen and naproxen did not reverse TNFα insulin resistance. Additionally, animals deficient in IKKβ expression exhibited improved insulin resistance over those with normal IKKβ expression.

Implications: These experiments indicate that the IKKβ complex is important in the development of insulin resistance. High doses of aspirin and other salicylate containing drugs inhibit the IKKβ complex resulting in lowered blood glucose and insulin levels. These findings implicate an inflammatory process in the pathogenesis of insulin resistance in obesity and type 2 diabetes. These studies provide important insights into the development of insulin resistance and may lead to improvements in treatment or possibly prevention of insulin resistance and the resulting development of type 2 diabetes.

Yuan M, Konstantopoulos N, Lee J, Hansen L, Li ZW, Karin M, and Shoelson SE: Reversal of obesity- and diet-induced insulin resistance with salicylates or targeted disruption of IKKβ. Science (in press 2001).

Forced Limb-use Studies in Rats May Have Implications for Parkinson's Disease

Background: Parkinson's Disease is a severe neurodegenerative disease characterized by progressive and severe muscle impairment which is caused by the loss of dopamine-producing nerve cells (neurons) in the substantia nigra region of the brain. Behavioral and neurological changes may delay or mask the appearance of symptoms until the neurological damage becomes extensive enough to overwhelm these compensating mechanisms. As the disease progresses, patients tend to rely more on less-affected limbs to make movement easier. Over time, conventional treatments lose their efficacy in relieving symptoms, movement becomes more difficult, and inactivity becomes more prominent.

Advance: Laboratory rats were surgically administered the nerve toxin, 6-hydroxydopamine, to one side of their brains resulting in the impairment of the forelimb on the opposite side of their bodies. The animals were fitted with casts on their unaffected forelimb making them use the affected limb to move and support their weight. Animals fitted with the casts within one day of the experimental procedure were able to use the leg normally once the casts were removed. In addition, all tests for dopamine concentration and metabolism were normal, suggesting a decrease in the degeneration of the dopamine producing neurons.

Implications: These findings suggest that physical therapy and exercise may have major effects on the quality of life for Parkinson's patients. Improvements in the movement of affected limbs should be expected, but more importantly, therapy may delay or prevent the loss of dopamine producing neurons, which is the goal of current treatments.

Tillerson JL, Cohen AD, Philhower J, Miller GW, Zigmond MJ, and Schallert T: Forced limb-use effects on the behavioral and neurochemical effects of 6-hydroxydopamine. Journal of Neuroscience 21: 4427-4435, 2001.

Controlling Taxol's Toxicity in Breast Cancer Treatment

Background: One of the most significant breakthroughs in breast cancer treatment is the chemotherapy agent, taxol. It is a highly toxic drug, but it is this very toxicity that enables it to kill breast cancer cells that have spread in the body. Women vary greatly in their tolerance of this drug and finding the correct dosage is one of the many challenges facing women when they undergo chemotherapy. At present, the procedure is to start a standard dose and then determine from a woman's reaction to the drug whether the dose is too high. Improved ways to individualize the dose would be of obvious benefit to women during this difficult time.

Advance: Like many compounds, taxol circulates in the body until it is broken down, or metabolized, by enzymes in the body and then subsequently excreted. Genes coding for these enzymes can have subtle variations, or polymorphisms, that can render the enzyme more, or less, capable of metabolizing drugs or foreign agents. If the polymorphism results in an enzyme with less activity, then the drug circulates much longer in the body than it would in normal people. Thus, what is considered a normal dose would effectively be too high in people with a less active metabolizing enzyme.

Two genetic polymorphisms were discovered in a drug-metabolizing enzyme CYP2C8 which is responsible for metabolism of the anticancer drug taxol in humans. One polymorphism (named CYP2C8*3) causes two amino acid substitutions in the protein. In laboratory tests *in vitro* using recombinant human enzymes, the polymorphism decreased metabolism of taxol dramatically. Genetic tests have been devised to test for these polymorphisms in human blood, and these tests will be used to examine whether these polymorphisms affect blood levels of taxol and its toxicity in breast cancer patients who are being treated therapeutically with taxol.

Implications: If clinical studies bear out these findings, oncologists will have a valuable tool in determining the correct and tolerable doses of taxol to administer to their patients.

Dai D, Zeldin D, Blaisdell JA, Chanas B, Coulter SJ, Ghanayem BI, and Goldstein JA: Genetic polymorphisms of human CYP2C8 and their effects on the metabolism of paclitaxel and arachidonic acid. Pharmacogenetics (in press 2001).

Combination Therapies for AIDS Patients – How Toxic are They?

Background: A retrovirus, the human immunodeficiency virus (HIV), exploded on the world's stage when it was found to cause the devastation known as acquired immunodeficiency syndrome (AIDS). Because AIDS patients have such severely impaired immune systems, they often die from opportunistic infections such as tuberculosis. Those suffering from infections are generally treated with combination therapies – one for treatment of AIDS and one for treatment of other existing infections. Although we now know the toxic effects of most anti-HIV drugs and most opportunistic infection drugs when administered separately, little is known about how they act in combination and which combination therapies would be least toxic.

Advance: Tuberculosis is a common opportunistic infection in HIV positive patients. Rifampicin is an antituberculosis drug used either alone or in combination with other antituberculosis drugs. Combination therapy with antituberculosis drugs such as Rifampicin and the AIDS drug, AZT, is a common procedure for treatment of HIV positive patients with tuberculosis. Toxic consequences of these combination therapies are not established. In a recent rodent study, rifampicin alone or AZT alone caused mild hematological (blood cells) toxicity. Rifampicin when administered in combination with AZT markedly increased the hematological toxicity in a mouse model.

Implications: Prolonging life and maintaining acceptable quality of life for HIV positive individuals will depend upon the use of combination therapies in the foreseeable future. Testing out these combinations in rodent models will enable us to determine the optimal drug regimens for maintaining life with the lowest possible side effects from these therapies.

National Institute of Environmental Health Sciences, 2001: Subchronic toxicity study of 3'-Azido-3'-deoxythymidine (AZT) and rifampicin combinations administered by gavage to B6C3F1 mice. National Institute of Environmental Health Sciences AIDS Therapeutics Toxicity Report No. 6. NIH Publication 01-4401. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. Research Triangle Park, NC.

Drug Treatment of Lead-exposed Children Does Not Improve Psychological Test Scores

Background: Lead, a common environmental contaminant found in household dusts and yard soil, pipe solder, old paint, and some ceramics, causes obvious health problems at high doses. The past two decades, however, have provided evidence that even relatively low blood lead levels (5-35 μg/dL) can lead to a 2- to 4-point IQ deficit for every 10 μg/dL of lead in blood, when the exposure occurs developmentally or in early life. Although these deficits are small, evidence also suggests that low blood lead levels translate into later problems in school, particularly decreased attention spans, reading disabilities, increased aggression as juveniles, and failure to graduate from high school. Although these studies have the confounding factor that much of the lead exposure occurs in inner-city and impoverished neighborhoods, where low socioeconomic status and low parental education can also negatively affect IQ, they nonetheless have led to a reassessment of what constitutes an "acceptable" blood lead level in children. In particular, many pediatricians are treating young children with low blood lead levels with the lead-removing chelating drug, succimer, in the hope that it will reverse the small reduction in IQ and later behavioral effects. A clinical trial was initiated to determine if this new, untested therapy was useful.

Advance: Succimer was found to lower blood lead levels, but did not improve test scores when used to treat low blood lead levels in children. Although drug treatment at age two with succimer lowered blood lead faster than placebo, as expected, it did not improve scores on psychological, behavioral and IQ tests when the children were followed until age five. The results of the trial show clearly that treatment after the fact does not undo the damage among 5 year olds. We must prevent these children from being exposed in the first place. While the children given succimer had more rapid drops in their blood lead, the differences in tests scores were small, inconsistent, and not statistically significant. The study was large enough to have detected an improved IQ score of less than 3 points, and no such improvement was seen.

Implications: The current practice of treating low-blood-lead-level children with succimer is unlikely to cause improvement in test scores. A better public health practice would be to prevent the exposure at the outset.

Rogan WJ, Dietrich KN, Ware JH, Dockery DW, Salganik M, Radcliffe J, Jones RL, Ragan NB, Chisholm JJ, and Rhoads GG: The effect of Chelation therapy with Succimer on neuropsychological development in children exposed to lead. The New England Journal of Medicine 344: 1421-1426, 2001.

Toxic Effects Caused by Drugs Used to Treat AIDS

Background: More than 36 million people are infected by the human immunodeficiency virus (HIV) worldwide with 5.3 million new infections occurring during 2000. Although antiviral therapy extends the life of individuals infected with HIV, the death toll continues to rise; three million people, the highest number since the epidemic began, died of AIDS in 2000. Potent antiviral medications reduce the rates of morbidity and mortality due to HIV. Long-term treatment with these drugs, however, frequently has unintended adverse health effects. Severe antiviral treatment-induced toxicity may occur from the continuous antiviral therapy required to keep the HIV infection under control. Research has shown that antiviral drugs can be toxic to the mitochondria in patients being treated for HIV infection. Mitochondria are cellular structures that supply the energy used by each cell. The drugs used to treat HIV infection block both HIV reverse transcriptase, an enzyme used by HIV to form DNA, and mitochondrial DNA gamma polymerase, an enzyme used by mitochondria to replicate or repair DNA. The cause of this toxicity is the inhibition or perturbation of mitochondrial DNA synthesis.

Advance: All of the currently approved antiviral drugs that were tested were incorporated into mitochondrial DNA by gamma polymerase, and all inhibited DNA synthesis to varying degrees. 3TC was one of the drugs least likely to be incorporated into DNA and yet was one of those most efficiently removed. This may explain the low mitochondrial toxicity induced in patients receiving 3TC. AZT was the least likely to be incorporated into DNA by gamma polymerase; but once incorporated, it was not efficiently removed from DNA. The inefficiency of gamma polymerase in removing AZT from DNA may help to explain the AZT-induced mitochondrial DNA depletion observed in HIV patients. AZT toxicity may be the combined effect of moderately efficient incorporation and very inefficient removal, resulting in its persistence in mitochondrial DNA. Additionally, a high concentration of AZT may inhibit gamma polymerase proofreading, thereby causing an increase in mitochondrial DNA mutations.

Implications: Drugs currently being used to treat HIV infection clearly result in compromised mitochondrial function due to inhibition of the mitochondrial DNA polymerase. Understanding the mechanism of mitochondrial toxicity will help in developing safe and effective antiviral medications.

Lim SE, and Copeland WC: Differential incorporation and removal of antiviral deoxynucleotides by human DNA polymerase _. Journal of Biological Chemistry (in press 2001).

Reducing Side Effects of Drugs – Drug Metabolism Variations Identified

Background: The Environmental Genome Project was established to identify gene variations in the human genome that make some people more resistant or susceptible to diseases induced by environmental agents. Scientists have known that people express differing levels of a family of enzymes known as cytochrome P450s based on their genetic makeup. The enzymes are responsible for metabolism of a wide variety of compounds, both those made by the body and those introduced from outside the body. Approximately 55 different genes have been identified that code for the various cytochrome P450s.

Advance: This paper describes the identification of variations in the gene for cytochrome P450-3A5 (CYP3A5). Members of the CYP3A family make up almost half of the total cytochromes found in liver tissue and are responsible for the metabolism of estrogens and many drugs, including HIV protease inhibitors, calcium channel blockers, cholesterol reducing agents, cancer chemotherapeutics, and transplant rejection drugs. The results indicate that the substitution of a single incorrect nucleotide, also known as a single nucleotide polymorphism, in the structure of the CYP3A5 gene disrupts the activity of the enzyme transcribed from that gene. Further genetic analyses demonstrated that only 30 percent of Caucasians and over 50 percent of African-Americans and Asians have the normal gene and produce normal levels of CYP3A5. These differences in expression are much larger than previously believed.

Implications: Based on these findings, the research team predicts many patients will eventually be screened for CYP3A5 activity. Those with low activity will likely have doses of chemotherapeutic and immune suppression drugs reduced to reduce associated toxicities and improve therapeutic responses. The ability to express CYP3A5 may prove to be one of the most important elements in population differences in drug metabolism and drug response.

Kuehl P, Zhang J, Lin Y, Lamba J, Assem M, Schuetz J, Watkins PB, Daly A, Wrighton SA, Hall SD, Maurel P, Relling M, Brimer C, Yasuda K, Venkataramanan R, Strom S, Thummel K, Boguski MS, and Schuetz E: Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. Nature Genetics 27: 383-391, 2001.

Regulation of Cartilage Induction

Background: Osteoarthritis is a common musculoskeletal disorder, characterized by joint pain, tenderness, and functional disability. Despite its prevalence, osteoarthritis remains a condition that is poorly understood and for which few therapeutic options are available. The repair of cartilage damage from degenerative diseases, such as osteoarthritis, represents a problem of major clinical significance. However, insufficiency of natural repair is common, resulting in persistent joint dysfunction. The introduction of therapeutic agents at the sites of cartilage damage offers exciting potential for initiating and accelerating repair processes. This advance describes the identification of a novel transcription factor that may represent a target for such therapeutic intervention.

Advance: Transcription factors are proteins that bind to DNA in a highly specific fashion and regulate the expression of groups of genes. Researchers have identified a transcription factor (NFATp) that appears to repress cartilage cell growth and differentiation in the adult animal. Few molecular regulators of cartilage formation have been identified, and the majority of these affect the embryonic development of cartilage. Studies using genetically engineered mice have shown that overexpression of the factor prevents the formation of cartilage, while loss of the factor results in spontaneous activation of cartilage differentiation. These results suggest that this newly identified factor is the first transcription factor described to control the differentiation of adult stem cell populations into cartilage.

Implications: The successful regeneration of articular cartilage has not yet been accomplished. Compounds that block the function of this novel transcription factor in cartilage may prove valuable in achieving sustained differentiation and growth of cartilage from adult stem cell populations. Such inhibitors may have potential therapeutic use in degenerative joint diseases such as osteoarthritis and rheumatoid arthritis, where cartilage has been destroyed.

Ranger AM, Gerstenfeld LC, Wang J, Kon T, Bae H, Gravallese EM, Glimcher MJ, and Glimcher LH: The nuclear factor of activated T cells (NFAT) transcription factor NFATp (NFATc2) is a repressor of chondrogenesis. Journal of Experimental Medicine 191: 9-21, 2000.

Insights into the Pathogenesis of Marfan Syndrome, a Heritable Disorder of Connective Tissue

Background: Marfan syndrome is a genetic disorder characterized by dislocation of the ocular lens, long bone overgrowth, and early death due to aortic rupture. Marfan syndrome results from mutations in the gene for fibrillin-1, a protein found in elastic fibers. Gene-targeting experiments in the mouse have shed new light on fibrillin 1 function. These experiments have documented the involvement of fibrillin 1 in maintaining tissue homeostasis, suggested the existence of a critical threshold of functional microfibrils for normal tissue strength.

Advance: New studies on tissue analysis of genetically engineered mice revealed cellular events that initiate destructive changes in the aortic vessel wall. The first detectable set of abnormalities included a change in appearance of the elastic fibers, the loss of cell attachment sites that are normally controlled by fibrillin-1, and a change in shape adopted by the vascular smooth muscle cells. Also, these cells displayed an abnormal pattern of protein synthesis, including the production of an enzyme known to degrade elastin. Ultimately, zones of elastic fiber thinning and fragmentation resulted. These data suggest that the loss of cell attachments signals a nonproductive program to synthesize and remodel an elastic matrix. This refined understanding of the pathogenesis of vascular disease in Marfan syndrome may facilitate the development of therapeutic strategies.

Implications: These data suggest that therapeutic strategies aimed at modulation of cellular phenotype and/or inhibition of protease activity may hold promise to preclude development of aortic disease in Marfan syndrome. It may be informative to determine whether the introduction of targeted mutations for the genes encoding certain degradative enzymes or overexpression of factors that inhibit these enzymes in the mouse model has the ability to abbreviate or abrogate vessel wall disease.

Bunton TE, Biery NJ, Myers L, Gayraud B, Ramirez R, and Dietz HC: Phenotypic alteration of vascular smooth muscle cells precedes elastolysis in a mouse model of Marfan syndrome. Circulation Research 88: 37-43, 2001.

Pyo R, Lee JK, Shipley M, Curci JA, Mao D, Ziporin SJ, Ennis TL, Shapiro SD, Senior RM, and Thompson RW: Targeted gene disruption of matrix matelloproteinase-9 (gelatinase B) suppresses development of experimental abdominal aortic aneurysms. Journal of Clinical Investigation 105: 1641-1649, 2000.

Gender, Catastrophizing, and Pain in Osteoarthritis

Background: Recently, there has been growing interest in gender differences in pain and disability, and increased recognition of the role gender can play in influencing the pain experience and treatment response. One psychological response to pain that might help account for the differences between men and women is catastrophizing. Catastrophizing is defined as a person's tendency to focus on and exaggerate how threatening the pain is, and the tendency to feel unable to cope with the pain. Several studies have shown that women engage in catastrophizing to a greater extent than do men. Osteoarthritis (OA) is a common form of arthritis in which pain is the most frequent symptom, and women are more likely to report OA pain than men. The primary goal of this study was to examine the relationship of gender to the experience of pain in people with OA. Women were expected to have higher levels of pain, pain behavior, and physical disability than men. Catastrophizing was examined as a variable that might explain these differences.

Advance: Researchers studied 72 men and 96 women with OA of the knee. Pain and physical disability, depression, and catastrophizing were measured using standard questionnaires. Pain behavior (for example, active rubbing of the knee; abnormally slow, stiff, interrupted, or rigid movement) was assessed using a behavior observation method. Women had significantly higher pain, physical disability, and total pain behaviors than men. Analyses revealed that once catastrophizing was taken into account the previously significant effects of gender were no longer found. In other words, the differences between women and men in pain and disability may be explained by the greater tendency of women to catastrophize.

Implications: The results of this study may have important implications for the management of pain. First, clinicians need to recognize that there may be important gender differences in the experience of pain, the display of pain behaviors, and physical disability in OA patients. Treatment may have different effects on pain and pain-related outcomes if one is treating men versus women having OA. Cognitive therapy or cognitive-behavioral therapy designed to reduce catastrophizing may be particularly useful in reducing pain and disability in patients who tend to catastrophize. Before intervening, however, clinicians need to consider the social context of catastrophizing and OA pain. In some circumstances, catastrophizing may have important and potentially desirable interpersonal consequences. Individuals who catastrophize may be signaling their distress to others and seeking help in coping with pain. These people may prefer an interpersonal approach to coping and to pain management, such as spouse-assisted coping skills training. The study findings underscore the importance of both gender and catastrophizing in understanding the OA pain experience and may have important implications for pain assessment and treatment.

Keefe FJ, Lefebvre JC, Egert JR, Affleck G, Sullivan MJ, and Caldwell DS: The relationship of gender to pain, pain behavior, and disability in osteoarthritis patients: the role of catastrophizing. Pain 87: 325-334, 2000.

Early Mortality in Systemic Lupus Erythematosus in Three Ethnic Groups

Background: The overall survival of patients with systemic lupus erythematosus (SLE) has improved dramatically over the last few decades. However, there are still patients who die relatively early in the course of their disease, either from very severe disease or from treatment-related complications. It is not clear whether poor outcome in SLE is related mainly to genetics, socioeconomic factors, or a combination of both. Moreover, most research has not involved patients from diverse ethnic or socioeconomic backgrounds. The LUMINA study (Lupus in Minority Populations, Nature vs. Nurture) is the first to study a multiethnic group of SLE patients over time to determine the factors associated with disease course and outcome.

Advance: Patients of Hispanic (Mexican- or Central-American ancestry), African-American, or Caucasian ethnicity, with confirmed SLE of 5 years duration or less, have been studied for 5 years. Several types of data were obtained: socioeconomic and demographic, clinical and immunologic, genetic, behavioral, and cultural. Income and number of persons in the household were used to define poverty according to the U.S. Federal government guidelines. Disease activity, disease duration, and disease damage were measured as well. Follow-up visits were conducted every 6 months for the first two years of the study, and yearly thereafter. At 5 years, 34 of 288 patients (11.8 percent) had died; 41.2 percent of deaths were mainly disease-related, 32.4 percent were mainly related to an infectious disease, and 17.6 percent were due to heart disease or stroke. Early mortality was not associated with genetic, immune, or behavioral variables. Variables consistently found to be related to early mortality were increased disease activity, increased disease damage, and poverty.

Implications: This study is the first to study Hispanic, African-American, and Caucasian ethnic groups with SLE simultaneously. The most important finding is that poverty and not ethnicity was the variable consistently found to predict early mortality. The most important variables influencing disease activity were socioeconomic and demographic rather than ethnic/racial or genetic. The findings are consistent with a body of literature that indicates that, regardless of the condition being studied, patients with a low socioeconomic status fare much worse than those with an overall better socioeconomic status. Special attention to these socioeconomic and demographic features is warranted when managing lupus patients. In addition to the pharmacologic therapy chosen, special emphasis should be placed on adherence to the regimen prescribed, identification of disease flare-ups or additional illnesses, family and social support, and the like.

Alarcón GS, McGwin GJr, Bastian HM, Roseman J, Lisse J, Fessler BJ, Friedman AW, and Reveille JD: Systemic lupus erythematosus in three ethnic groups. VIII. Predictors of early mortality in the LUMINA cohort. LUMINA Study Group. Arthritis and Rheumatism 45: 191-202, 2001.

Activated Immune Cells in Pathogenesis of Duchenne Muscular Dystrophy

Background: Duchenne Muscular Dystrophy (DMD) results when the muscle protein dystrophin is absent or impaired. Normal dystrophin is one of the largest proteins known and is the product of a similarly large gene, which is susceptible to a high frequency of spontaneous mutations. Dystrophin is part of a complex structure involving several other protein components. Defects in how this complex structure is assembled lead to structural problems that can disrupt the integrity of the outer membrane of muscle cells, resulting eventually in degeneration. There are many components in the pathological cascade that leads to the death of dystrophic muscle. The effectiveness of an anti-inflammatory drug, prednisone, in improving muscle strength and mass in DMD indicates that the problem is more complicated than a simple mechanical defect model. Other work also suggests that there is increased inflammation in dystrophin-deficient muscles.

Advance: Researchers tested whether certain immune cells had a significant role in the pathogenesis of DMD. Comparing normal and *mdx* mice (an animal model of DMD), they found that activated T cells (a type of immune cell) occur with a significantly higher frequency in the blood and muscle of the diseased animals. However, the frequency of activated T cells was not elevated in the lymph nodes of the *mdx* mice. This suggests that T cell activation is muscle-specific. Further, removing activated T cells from *mdx* mice significantly lowered visible pathology. When researchers reduced the concentration of two types of activated T cells (called CD4+ and CD8+), they lowered the amount of discernable pathology (by 61 percent and 75 percnet, respectively). The investigators found that transfer of *mdx* immune cells in combination with muscle extracts resulted in muscle pathology in previously healthy mice. These results indicate that T cells promote the *mdx* pathology and suggest that immune-based therapies may provide benefit to DMD patients.

Implications: The identification of the immune system as a contributing factor in the pathology associated with dystrophin that is defective or missing suggests the possibility for new therapeutic approaches for treatment. Characterization and isolation of muscle reactive T cells might allow for the identification of the antigenic protein. This knowledge might be used to induce specific tolerance, as is being tested in treatment for autoimmune disorders. Additional therapeutic approaches can be developed when the specific mechanisms leading to T cell activation and the specific substances involved in the pathogenic process are identified.

Spencer MJ, Montecino-Rodriguez E, Dorshkind, K, and Tidball JG: Helper (CD4+) and Cytotoxic (CD8+) T cells promote the pathology of dystrophin-deficient muscle. Clinical Immunology 98: 235-243, 2001.

Skin and Muscle Coverage of Severe Leg Injuries

Background: High energy injuries of the legs, as when a pedestrian is hit by a car, are common, costly, and potentially very disabling. Treatment of these injuries may require multiple surgeries, prolonged hospitalizations and rehabilitation, and may result in an amputation. In addition, these injuries are a treatment challenge for the orthopaedic surgeon, with uncertainty as to what is the best treatment for a particular type of injury. A major problem with this type of trauma are severe injuries to the skin and muscle overlying the injured leg. Coverage of these injuries, with or without an associated fracture, with healthy muscle and skin is required to prevent infection and for bone healing. The two most common ways to provide skin/muscle coverage is with a rotational flap (rotate healthy skin and muscle into the area of the injury) or with a free flap (skin and muscle from a distant site, with attached blood vessels, are moved to the site of injury).

Advance: The purpose of this study was to identify the factors that may influence the development of wound complications (graft failure and infection) and therefore the success or failure of rotational flaps *versus* free flaps in the treatment of these injuries. Six hundred-and-one patients were studied at eight trauma centers throughout the U.S. They found that: (1) patients treated with a free flap sustained a more severe injury to the overlying skin and muscle; (2) patients treated with a free flap were more likely to have associated fractures; (3) patients treated with a rotational flap were more likely to have associated injuries to other parts of the body (i.e., head injury); (4) contrary to other studies, free flaps were not associated with more wound complications than rotational flaps; they found fewer such complication in the free flap group; and (5) contrary to other studies, timing of surgery to provide skin/muscle coverage was not a determinant of wound complications following severe leg injury.

Implications: This study is the first prospective comparison of wound complications by the type of flap used after high energy trauma of the leg. In addition, it is the first such study to take the effects of injury, treatment, and patient characteristics into consideration when attempting to identify factors that may lead to wound problems following these injuries. The findings suggest that for severe injuries, use of a free flap is associated with fewer wound complications than with a rotational flap. These findings may change the way that these injuries are treated. In addition, if validated, they may result in fewer complications, with lower medical costs and improved function and quality of life following these injuries.

Pollock AN, McCarthy ML, and Burgess AR: Short term wound complications after application of flaps for coverage of traumatic soft-tissue defects about the tibia. The Journal of Bone and Joint Surgery 82-A12: 1681-1691, 2000.

Investigating the Treatment of Alopecia Areata in Mouse Model Systems

Background: Alopecia areata is a non-scarring reversible disorder that is the second most common cause of hair loss in humans. It is thought to be an autoimmune disease in which the hair follicle is the target of the body's immune system. This autoimmunity model has been the basis of many of the treatments for alopecia areata, but the exact method by which these treatments are effective is not well known. Part of the problem was the lack of good animal models for alopecia areata in which to not only evaluate treatments that seem successful in man but also screen potential new treatments. In recent years, an animal model system for alopecia areata has been described. This system is the C3H/HeJ mouse which does develop an alopecia areata-like picture mediated by autoimmune attack on the hair follicle.

Advance: Since the alopecia areata mouse develops the disease in a predictable time sequence, it is not only possible to treat established disease but also to treat mice prior to the onset of the disease to see whether the disease can be prevented or delayed. A study was performed in which antibodies were given to the mice to try to inhibit the autoimmune process underlying the alopecia areata. In the animals so treated, the onset of hair loss was delayed somewhat and the extent of hair loss reduced by about half. When the skin was biopsied, it was determined that the treatment resulted in a marked reduction in the white cells surrounding the hair follicles. This finding implies that the treatment reduced the autoimmune attack on the hair follicle and, therefore, delayed and reduced the severity of the resultant alopecia areata.

Among the widely used treatments for alopecia areata in humans is the induction of allergic contact dermatitis by the use of a locally applied chemical called squaric acid dibutylester. This material was investigated in the mouse model of alopecia areata. The chemical was applied to one side of the alopecia areata mouse but not to the other. In nine of eleven experimental mice, the hair regrew on the treated side only and was associated with a reduction in inflammation and other indicators of reduced levels of local destruction of the hair follicle.

Implications: These studies further support the autoimmune theory of alopecia areata. They also demonstrate that this C3H/HeJ alopecia areata mouse may be used to investigate the mechanism by which treatments may work in alopecia areata in humans and may be used as a screening model system for developing new treatment approaches for alopecia areata in man.

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Treatment for Psoriasis

Background: Psoriasis is one of the most common skin diseases, affecting several million American citizens. The disease varies in its severity and clearly has a genetic basis although the predisposing gene or genes have not been isolated. Treatment has been reasonably successful for most patients but some of the treatments have potentially serious side effects, particularly after long-term use. An advance in the treatment of psoriasis developed and introduced into the market several years ago was the use of topical vitamin D derivatives now marketed in the U.S. as Dovonex. Other potentially more effective and/or safer derivatives of vitamin D continue to be investigated.

Advance: A new type of vitamin D (called hexafluoro-1,25-dihydroxyvitamin D3) was evaluated for its efficacy in the treatment of psoriasis. Fifteen patients with plaque-type psoriasis were enrolled in a study that compared the use of the drug in comparison with a placebo (a substance that did not contain the drug) on the right and left side of the body. Using severity scores, the treated side showed a decrease in psoriasis severity of 85 percent while the placebo side showed a decrease of 45 percent. This result was highly statistically significant. Twelve of the patients subsequently applied the active agent to all lesions and eleven of the twelve showed moderate to excellent improvement. The only adverse effect was mild irritation in two patients, which was resolved with continued treatment.

Implications: The genetic basis for psoriasis is likely to be found in the near future and our understanding of the pathophysiology of the disease will allow the development of new therapies in the future. However, at the present time, treatment typically consists of topical cortocosteroids, tars and other agents in the mild to moderate cases and a variety of other treatments, some of which have significant side effects, for the more severe cases. There will probably always be a place for topical treatment of mild to moderate psoriasis as long as the topical agents are relatively risk free and effective. The currently available vitamin D derivatives are reasonably effective but have not made as great an impact on the treatment of the disease as might be hoped. This new derivative, particularly since it is a once a day application, may prove more useful than the currently available modalities.

Durakovic C, Malabanan A, and Holick MF: Rationale for use and clinical responsiveness of hexafluoro-1,25-dihydroxyvitamin D3 for the treatment of plaque psoriasis: a pilot study. British Journal of Dermatology 144: 500-506, 2001.

New Therapy for Lupus Tested in Mice

Background: Lupus is an autoimmune disease that can affect many parts of the body, including the joints, skin, kidneys, heart, lungs, blood vessels, and brain. Many more women than men have lupus. It is three times more common in African-American women than in Caucasian women and is also more common in Hispanic, Asian, and Native American women. Lupus is a challenging disease due to its range of symptoms and irregular course. Potent immunosuppressive drugs (drugs that suppress the immune system) are often the only effective treatment to control lupus, but these drugs have their own harmful effects. New therapies are being sought for lupus.

Advance: Investigators at a research center have demonstrated a new approach for controlling the symptoms of lupus. Using a mouse model for lupus, they were able to delay the onset of kidney damage and to block increased antibodies characteristic of lupus. The approach the investigators used was to synthesize a small protein, called consensus peptide, that mimicked the binding regions of a specific group of proteins, IgG antibodies to DNA (a sspecific type of autoantibodies). These IgG anti-DNA antibodies are characteristic of lupus. Stimulation of T-lymphocytes in lupus leads to overproduction of autoantibodies. However, when the consensus peptide was injected into the mice, this response was not found. Consensus peptide had produced immune tolerance. Tolerance is defined as a selective block in the immune response to particular chemicals called antigens. In these studies the binding region of the IgG anti-DNA antibodies is the antigen.

Implications: This is the first report of the potential clinical utility of a unique synthetic peptide designed to interfere with the lupus autoimmune response. The administration of the consensus peptide was effective in producing immune tolerance even after the disease was present. A similar strategy may be useful for patients with lupus.

Hahn BH, Singh RR, Wong WK, Tsao BP, Bulpitt K, and Ebling FM: Treatment with a consensus peptide based on amino acid sequences in autoantibodies prevents T cell activation by autoantigens and delays onset in murine Lupus. Arthritis and Rheumatism 44: 432-441, 2001.

Administration of Parathyroid Hormone Reverses Bone Loss in Osteoporotic Women

Background: Our currently available osteoporosis therapies work by reducing bone turnover. These therapies produce only modest increases in bone mass and reduce the risk of fractures to the spine and hip by no more than 40-60 percent. New therapies are needed that will stimulate bone formation and increase bone mass more substantially.

Advance: Parathyroid hormone is capable of both stimulating bone formation and of suppressing bone formation. Researchers at a research center have shown that administration of parathyroid hormone can dramatically reduce the incidence of vertebral fractures in women who are on hormone replace therapy. In a trial lasting three years, women who were on hormone replacement therapy for osteoporosis were also given parathyroid hormone injections daily for three years. The bone mass of women treated with parathyroid hormone increased in the vertebrae and hip over those values measured in women receiving only hormone replacement therapy. Loss of vertebral bone results in collapse of the supporting structure of the spine, leading to a decrease in height and deformity of the chest. This process was dramatically reduced in women receiving parathyroid hormone.

Implications: Osteoporosis is a major health risk for 28 million Americans. In the U.S. today, 10 million individuals already have osteoporosis and 18 million more have low bone mass, placing them at increased risk for this disease. American women are four times more likely to develop osteoporosis than men. One out of every two women and one in eight men over 50 will have an osteoporosis-related fracture in her or his lifetime. Current therapies at best stop further bone loss. The finding that parathyroid hormone administration can increase bone mass may lead to therapies that rebuild lost bone thereby reducing spinal deformity and hip fracture in older Americans.

Cosman F, Nieves J, Woelfert L, Formica C, Gordon S, Shen V, and Lindsay R: Parathyroid hormone added to established hormone therapy: effects on vertebral fracture and maintenance of bone mass after parathyroid hormone withdrawal. Journal of Bone and Mineral Research 14: 925-931, 2001.

Mechanism of Parathyroid Hormone to Increase Bone Mass Clarified

Background: Parathyroid hormone is an important regulator of calcium in the body. One action is to stimulate bone-forming cells, osteoblasts. This stimulation is accomplished through a receptor for parathyroid hormone on osteoblasts resulting in more bone formation. However, it is also known that parathyroid hormone can cause increased numbers of cells that degrade bone, cells called osteoclasts. The factors underlying these dual actions of parathyroid hormone are not completely understood.

Advance: Investigators at a research center have produced a mouse strain with a receptor for parathyroid hormone that is always "turned on," whether or not parathyroid hormone is present. These mice were found to have an increase in bone mass resulting from an increase in the type of bone found inside the structure, trabecular bone. Trabecular bone is an elaborate matrix rather than a solid structure. The matrix structure lends strength without undue mass. It is the matrix structure that is lost in osteoporosis. The outside portion of the bone, cortical bone, is a more solid structure. In these genetically altered mice, the cortical bone decreased. Analysis of the bone indicated that osteoblasts, the bone forming cells, were greatly increased in the trabecular portion of the bone but greatly decreased in the cortical bone. The numbers of bone degrading cells, osteoclasts, were also increased.

Implications: Parathyroid hormone is an important promoter of bone formation. Studies are underway to determine how effective administration of parathyroid hormone may be in reversing or at least arresting osteoporosis. These studies clarify the role of the parathyroid receptor in mediating both bone-forming and bone-dissolving actions of the hormone. Alternative agents may be found to stimulate the parathyroid receptor and reverse osteoporosis.

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Treating Insomnia with Cognitive Behavioral Therapy, Not Medications

Background: Persistent primary insomnia (PPI) is a disorder of middle-stage sleep maintenance that affects about 5 percent of the general population and 20 percent of patients who present clinically for treatment of sleep-related complaints. Such insomnia is predictive of the development of clinical depression and associated with increased use of health care services. Though most commonly treated with sedative hypnotic or antidepressant medications, long-term use of these drugs is associated with various adverse side effects and patients typically relapse into prior insomnia patterns after discontinuing their use. Behavioral interventions designed to correct habits that disrupt sleep and perpetuate insomnia have proven both effective and more durable than medication approaches in treating patients with problems of initial sleep onset, but results with PPI patients have been mixed. Several studies have suggested that combining cognitive therapy (which addresses attitudes and psychoeducation about sleep) with the straightforward behavioral techniques is a more comprehensive approach that is effective with both sleep-onset and sleep-maintenance problems, and more durable in effect than medications. However, comparisons of such a hybrid cognitive-behavioral therapy (CBT) for sleep have not been conducted to demonstrate its superiority to a simpler behavioral approach or to a non-medication psychotherapeutic placebo treatment.

Advance: In this study, 75 patients with PPI were assigned randomly to 6 weeks of treatment with a) a hybrid CBT involving sleep education, stimulus control methods, and time-in-bed restrictions; b) progressive muscle relaxation training; or c) a quasi-desensitization approach that constituted a behavioral placebo treatment relative to PPI. Patients were assessed on multiple sleep outcome measures, and followed up 6 months after completion of treatment. The results indicated that CBT led to more improvement on most sleep measures, and a greater normalization of sleep and subjective symptoms. For example, the extent of reduction in (middle and terminal stage) wake time after sleep onset (WASO) averaged 54 percent for patients treated with CBT, versus 16 percent for those receiving relaxation training and 12 percent for those in the behavioral placebo condition. In addition, the CBT-treated patients in this trial showed larger changes in dysfunctional attitudes toward sleep, as measured on an attitudinal questionnaire measure. The treatment gains seen during acute treatment tended to be well maintained after 6 months.

Implications: A sleep-oriented CBT appears to be an efficacious intervention for PPI and offers the added benefit of reducing the number of medications prescribed to many middle-age and older individuals. Even when compared with less specific or less comprehensive kinds of psychotherapeutic approach, CBT led to significantly greater and clinically meaningful sleep improvements within 6 weeks, and the improvements appeared to endure through the following 6 months. There is suggestive evidence that this intervention is influencing essential mechanisms involved in the development and persistence of sleep-maintenance difficulties.

Edinger JD, Wohlgemuth WK, Radtke RA, Marsh GR, and Quillian RE: Cognitive behavioral therapy for treatment of chronic primary insomnia: A randomized controlled trial. The Journal of the American Medical Association 285: 1856-1864, 2001.

Edinger JD, Wohlgemuth WK, Radtke RA, Marsh GR, and Quillian RE: Does cognitive-behavioral insomnia therapy alter dysfunctional beliefs about sleep? Sleep (in press 2001).

Parsing PACT: What Are the Critical Components of Holistic Community Care for SMI?

Background: Programs of Assertive Community Treatment (PACT) for persons discharged from psychiatric inpatient facilities have been shown to be highly effective in preventing readmissions and improving quality of life. PACT programs include assertive engagement of the client, delivery of services in client-based settings, multidisciplinary teams with shared caseloads, 24/7 team availability, and individualized plans of care. Although the program is cost effective when implemented as developed, PACT and similar multicomponent community-based service options are organizationally complex and difficult to implement as designed. What has been needed is information about how components of PACT work.

Advance: New research, conducted by three teams of researchers working in geographically and culturally diverse locations, has examined elements of community-based rehabilitation programs for people with severe mental illness (SMI). The key elements they have identified are:

- Clients' functioning improves most if they receive services over the long-term from involved staff who recognize that their needs are chronic, but change over time.

- Clients are more likely to become and stay employed if rehabilitation services are: (a) provided in the community and not in a clinic or day treatment facility and (b) provided by a full-time employment specialist and not by staff with mixed roles.

- Clients' physical health status is critical to success in community settings. Poor general health is associated with lack of work motivation, low self-esteem, inability to work, and poor self-reports of functioning. Psychiatric symptoms had a minimal association with community functioning outcomes.

- Dually-diagnosed clients (with a substance abuse disorder) need residential treatment where abstinence can be maintained and new behaviors can be learned and supported.

Implications: Community-based care for people with severe mental disorders has been recognized in the policy arena as requiring urgent attention. On June 7, 1999, the Director of the Health Care Financing Administration advised State Medicaid directors that they could use Medicaid funding to support assertive community treatment programs. In June 2001, legislation was introduced in the U.S. House of Representatives to allow States to invest in such community based programs. Clearly, not all communities can implement all the components of the original PACT model. But this research has begun to identify key components for successful community services: involved staff, long-term inclusion in services, employment specialists working with clients in community settings, good basic physical health care, and longer term residential treatment for dually diagnosed clients.

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St. John's Wort May Interfere with the Effectiveness of Prescription Medications

Background: St. John's wort is an over the counter herbal remedy commonly used to alleviate symptoms of depression. Individuals taking the compound have demonstrated seemingly negligible side effects. But, recently, there is evidence that St. John's wort can be problematic when taken in conjunction with prescription medications. For instance, two heart transplant patients suffered acute rejection of tissues following commencement with St. John's wort; the levels of cyclosporin, an immunosuppressant to prevent tissue rejection, were half the appropriate amount due to a metabolic interaction of the two drugs. Additionally, women taking oral contraceptives in conjunction with St. John's wort have reported break-through bleeding, indicating that the pill is not appropriately efficacious. Furthermore, St. John's wort seems to significantly reduce plasma indivir levels in HIV infected patients who take the reverse transcriptase inhibitor as part of their therapy.

Advance: Scientists have come closer to understanding some mechanistic actions of St. John's wort. It appears that one component of the herbal remedy, called hyperforin, binds to a newly identified receptor of the steroid/thyroid hormone family, called the pregnane X receptor (PXR), and consequently, induces expression of CYP3A4 in the liver of humans. CYP3A4 is an enzyme critical not only for the degradation of various compounds and toxins, but also for metabolizing drugs. It is estimated that CYP3A4 is responsible for metabolizing over 50 percent of all drugs.

Implications: Individuals should use St. John's wort with caution when taking medications because it could effectively inactivate the prescription medication. Furthermore, in terms of drug development, researchers can now look to identify drugs, like hyperforin, that have anti-depressant action but do not stimulate the PXR liver receptor.

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Medication and Psychotherapy Effective in Treating Children and Adolescents With Anxiety Disorders

Background: Anxiety disorders are the most common mental health disorders among children and adolescents, with an estimated prevalence rate of about 13 percent for 9-17 year olds. An anxiety disorder differs significantly from normal, developmental anxiety, and is accompanied by substantial interference in usual social activities. In many cases, these disorders are transient, but increase the risk for developing anxiety and depressive disorders in adulthood. It is not currently possible to predict which children will outgrow an anxiety disorder and which will continue to have anxiety or develop depression later in life. Research has shown that a 'cognitive-behavioral therapy', a form of psychotherapy, is an efficacious treatment for these children. Medications, such as the selective serotonin re-uptake inhibitors, have been shown to be efficacious in adults with anxiety disorders, and are prescribed to children in practice settings. However, their efficacy and safety in youths had not been demonstrated in a well-designed clinical trial.

Advance: Results from a multi-site, placebo-controlled clinical trial of fluvoxamine conducted in 128 youths aged 6-17 years indicate that this medication is highly efficacious for the treatment of anxiety disorders in children and adolescents. The study subjects had diagnoses of social phobia, generalized anxiety, or separation anxiety disorder. They were enrolled at 5 sites of the Research Units on Pediatric Psychopharmacology network. Following a 3-week evaluation period during which education and supportive therapy were provided, those subjects who had not shown signs of improvement were randomly assigned to fluvoxamine or placebo for 8 weeks. The trial was "double blind," meaning that neither the child nor the treating psychiatrist knew treatment assignment. At the end of the trial, 76 percent of the youths assigned to fluvoxamine were improved, in contrast to 29 percent of those on placebo. The safety of fluvoxamine was in general very good, although abdominal discomfort was reported more frequently than with placebo and 5 children (8 percent) discontinued fluvoxamine for adverse events such as sedation, gastric upset, or hyperactivity.

Implications: Findings support the use of fluvoxamine in the treatment of children and adolescents with anxiety disorders characterized by significant impairment in functioning. The results are limited to the short-term duration of the study, although a follow-up of the study sample will obtain information on the maintenance of treatment effects and extended safety. Now, efficacious psychosocial and pharmacological treatments are available, and treatments available to young people with disorders may be tailored to specific needs.

The Research Unit on Pediatric Psychopharmacology Anxiety Study Group: Fluvoxamine for the treatment of anxiety disorders in children and adolescents. The New England Journal of Medicine 344: 1279-1295, 2001.

Improving Chances for Employment: Negative Symptom/Positive Symptom Reductions in Schizophrenia

Background: The massive disability burden that stems from schizophrenia is evident in data showing that 70- to 90 percent of persons with the illness are not employed at any given time, and a majority of those who are employed work part-time or are in non-competitive situations such as sheltered workshops. Previous studies with small samples of clinic patients have suggested that negative symptoms – that is limited speech, flat or unexpressive mood, lack of motivation, and impaired attention – are stronger predictors of employment difficulties and poor social functioning than are such positive symptoms as auditory hallucinations, delusions, and illogical thought. Other problematic symptoms include depression and side effects of antipsychotic medications, which can affect motor function and physical appearance. Identifying improvements in treatment that would ameliorate the most troublesome symptoms and, in turn, enhance employment outcomes is a high priority challenge.

Advance: Researchers recently analyzed the relationships among treatment, symptoms, and employment outcomes, in an attempt to predict changes in rates of different types of employment that might result from reductions in symptom levels. The data come from a sample 1,643 adults with a schizophrenia diagnosis participating in a longitudinal study of treatment and outcomes (the Schizophrenia Care and Assessment Program, SCAP) in six localities in the U.S. Three employment measures were used: not employed, employed in a sheltered or supported job, and employed in a non-supported job. The symptom measures assessed the severity of positive and negative symptoms, comorbid depression, and medication side effects. Of these four categories, negative symptoms had the most substantial adverse effect on employment. The analysis showed that a 20 percent reduction in negative symptoms from the median would increase the mean rate of unsupported employment by 2 percentage points, to 11.6 percent, compared to an 0.26 percent increase for reducing symptoms of depression, an 0.4 percent increase for reducing positive symptoms, and an 0.27 percent increase from ameliorating the motor side effects of medications. Overall, the results indicate that even with treatment improvements that would lead to 40 percent reductions in all categories of symptoms, the rate of non-supported employment among people with schizophrenia would remain quite low, and only one-third of consumers would work for pay.

Implications: Improved treatments that result in reduced symptom levels will increase rates of employment among people with schizophrenia, but large effects on employment probably also require more effective rehabilitative therapies that target improvements in functioning. Expansions of supported employment opportunities and removal of work disincentives in public income-support programs are two additional measures that may help to increase employment participation.

Slade E, and Salkever D: Symptom effects on employment in a structural model of mental illness and treatment: analysis of patients with schizophrenia. Journal of Mental Health Policy and Economics (in press 2001).

Reducing Individual and Societal Burden of Depression: Results from a Community Primary Care Intervention Trial

Background: Depression is a leading cause of disability and reduced quality of life worldwide. Many depressed persons in the U.S. receive care from a general medical doctor rather than a specialist; but due to low rates of recognition of depression and low application of national guidelines, only 25 percent of primary care patients with depression receive recommended treatments. Prior studies have shown that models of care between generalists and specialists can improve the health of depressed primary care patients over at least several months, but broader impact on outcomes like employment have been uncertain. Additionally, it has not been clear that intervention programs are feasible for typical, community-based practices remote from academic centers.

Advance: A randomized trial of practice interventions to improve quality of care for depression showed that typical community-based practices can implement a structured program, although different practices vary in their implementation of different components. These range from training expert clinical leaders to education of clinicians and patients and providing resources for ongoing medication management. When practices implement their own programs locally, clinical, quality of life and employment outcomes improve over a full year of follow-up. In addition, a program like this that includes support for access to effective psychotherapy for depression can improve quality of life outcomes for nearly two years. This is a very long follow-up time for demonstrating improvement for any kind of treatment program for depression. The effect on employment was also substantial – a 5-percentage point advantage in employment retention for the intervention group has relevant positive implications for employers, given the high prevalence of depressive disorders in community samples.

Implications: Feasible practice-based interventions that support practices and patients in meeting good standards of care for depression at the local level can improve patient outcomes up to two years later, and offer broad gains for patients and society through improved health, quality of life, and more stable employment.

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Improved Diagnosis of Ataxia May Identify a Treatable Subtype

Background: Ataxia refers to a loss of movement coordination that can be severely disabling. Ataxias may be acquired, inherited, or result from developmental brain malformations. Trauma, infections, vascular events, brain tumors, metabolic disorders, toxins, and loss of the electrical insulation that covers nerve fibers may all cause acquired ataxias. The inherited ataxias are equally diverse in cause, reflecting defects in many different genes. A specific type of gene defect called a trinucleotide repeat expansion mutation causes several of the inherited ataxias, including Friedreich's ataxia and spinocerebellar ataxia types 1,2,3, 6,7,8 and 12, but in other cases different types of gene defects are involved or the cause of ataxia is unknown. With the exception of ataxias due to protein deficiency, such as isolated vitamin E deficiency and abetalipoproteinemia, most are resistant to treatment.

Advance: A new study examining six patients with unexplained, inherited ataxia and seizures found defects in a vitamin-like substance called coenzyme Q10, or CoQ10. This coenzyme serves as an antioxidant that protects cells from damage by free radicals generated as a byproduct of the chemical processes by which cells process energy. The amount of CoQ10 in the ataxic patients ranged from 65-74 percent less than normal. When researchers provided CoQ10 supplements in the diet, all six patients responded with improved coordination, increased strength, and less frequent seizures. Of the six patients, five were initially wheelchair-bound. Following CoQ10 supplementation these patients were able to stand and move with walkers.

Implications: The many inherited ataxias have long defied attempts at rational diagnosis and classification. In recent years, however, more than a dozen different genes have been identified that, when defective, can cause ataxia, and the diagnostic picture is beginning to clear. The cumulative results suggest that oxidative damage could be a key factor in many forms of ataxia. The identification of a subtype of ataxia caused by CoQ10 deficiency provides new knowledge about the potential causes of ataxia as well as a means to diagnose and alleviate symptoms when ataxia is caused by this vitamin deficiency.

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New Understanding of Inflammatory Pain

Background: Scientists are continuing to unravel the complex sequence of events that lead to inflammatory pain. In one critical step, inflammation turns on an enzyme called COX-2 at the site of pain. COX-2 makes substances called prostaglandins that increase the sensitivity of nerves to pain. Drugs that prevent COX-2 from making prostaglandins are widely used as pain medications but do not completely solve the problem. Inflammation can lead to increased pain sensitivity in neighboring undamaged tissue and is accompanied by general feelings of diffuse muscle and joint pain, fever, lethargy and loss of appetite. We are only beginning to understand how local inflammation leads to these more widespread problems.

Advance: Scientists studying inflammatory pain in rats have discovered that inflammation regulates the COX-2 enzyme within the spinal cord and brain as well as at the local site of inflammation. COX-2 produces prostaglandins in the brain and spinal cord that contribute to the increased pain sensitivity beyond the local site of inflammation. Researchers identified a cascade of steps, with each identified signaling chemical leading to the release of another, that underlies these central pain processes. Besides COX-2 and prostaglandin E2, these chemicals also include, for example, interleukin-1_, a chemical first identified for its role as an inflammatory signal released by cells of the immune system. The research team injected drugs directly into the spinal cord that blocked steps in this process without affecting the local site of inflammation. The drug treatments reduced inflammatory pain, clearly demonstrating that these central events are important factors in pain.

Implications: Developing drugs that interrupt the pain signals in the brain and spinal cord should lead to more effective control of pain, particularly the increased pain sensitivity to neighboring tissue. Many currently used drugs, such as COX-2 inhibitors, do not go through the blood-brain barrier, a natural protective system that keeps many substances out of the brain and spinal cord. These experimental findings also point towards remedies for the more general symptoms, such as fever, lethargy, and loss of appetite, that often accompany infection. Previous research has suggested that chemical signals, such as interleukins, can act in the brain to produce these symptoms.

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Learning From "Negative" Clinical Trials

Background: Clinical trials are the gold standard for testing whether a therapy or preventive measure really works, or works better than the best proven options. Among the ethical requirements for clinical trials is the principle of "equipoise." That is, well-informed experts should be uncertain which option is best for patients before a trial is conducted to compare those options. Otherwise, patients might be denied appropriate treatment or subjected to unjustified risk. For this reason, many trials find that a new therapy is not effective. Nevertheless, negative trials still provide valuable information.

Advance: A few recent clinical trials for neurological disorders illustrate how negative results can stimulate progress. The first controlled trial of brain transplants of fetal tissue to replace lost dopamine nerve cells in Parkinson's disease was negative, in that the primary measure did not indicate a benefit and some patients showed serious untoward effects. However, the trial clearly showed that cells transplanted into the brain can survive, make dopamine, and affect behavior. A trial of a different method of fetal tissue transplantation is underway, and animal research, alerted to the problems, can focus on better ways to control the outcome from transplantation. Similarly, two recent trials for multiple sclerosis confirm a new therapeutic strategy in principle, but demonstrate the need to refine the treatment. In both trials, a custom made molecule (a peptide) was designed to alter the attack by patients' immune systems on their own brain proteins. The results confirmed that the researchers had correctly identified which protein is critical in the disease and could affect the immune system response, but suggested lower doses of the peptide, or a less potent peptide might be better. In another example, a large, well-controlled trial, unlike previous smaller studies, found that hypothermia (cooling) did not improve outcome overall from severe brain injury. The results did, however, point to subgroups for whom the procedure might be more promising. Finally, preliminary results from the Women's Estrogen for Stroke Trial (WEST) suggest that estrogen replacement therapy may not reduce the likelihood of a new stroke. If the final results confirm this finding, the information will help physicians guide women in the complex decisions surrounding estrogen replacement therapy.

Implications: Although brain disorders have always been among the most difficult challenges for medicine, NIH has led positive clinical trials that have improved treatment or prevention of stroke, spinal cord injury, multiple sclerosis, epilepsy, Parkinson's Disease, and many other disorders. Advances in basic and clinical neuroscience are leading to an era when many more options for testing in clinical trials are coming forward than ever before. NIH is adapting with procedures designed to ensure that clinical trials move forward expeditiously, respect the ethical concerns, and are well-designed so that even a negative result can move toward better treatment and prevention of diseases of the brain and nervous system.

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Moving Towards Drugs for Prion Diseases

Background: Prion diseases include Creutzfeldt-Jakob disease (CJD) in people and bovine spongiform encephalopathy (mad cow disease) in animals. Although the incubation time for CJD may be decades, once symptoms appear the destruction of the brain progresses rapidly, typically to death within one year. CJD presents a scientific puzzle because the disease can be spontaneous, inherited, or infectious, and the agent responsible is not a conventional virus or bacterium. NIH scientists have played a major role in unraveling this mystery, as recognized by two Nobel prizes. Our current understanding is that CJD, and related diseases, result from a mis-folded version of a normal brain protein, called a prion. The abnormally shaped proteins draw normal prion proteins into the abnormal conformation, somewhat like a seed crystal forms a larger crystal. This background has been essential for confronting the public health issues surrounding mad cow disease and the new variant form of CJD, which about 100 people in Europe have contracted from consuming contaminated products.

Advance: There is no known treatment that slows the progression of CJD. Based on the understanding of the disease process, researchers developed a cell culture screening test for compounds that might prevent the formation of the abnormal prion aggregates or help cells clear those that already exist. The scientists focused on compounds that are known to cross the blood-brain barrier, which prevents harmful substances and many potentially therapeutic drugs from entering the brain from the general circulation. The screening strategy rationally applied chemical structural knowledge about prion aggregation to select candidate drugs. Two drugs effective in these cell culture tests are already approved for other medical uses. Chlopromazine has been used for the treatment of schizophrenia since the 1950's. Quinacrine (or atabrine), which was widely used during World War II for malaria, was even more potent in cell culture but does not cross the blood brain barrier as easily.

Implications: Because these drugs are already approved for human use, it may be possible to move quickly toward testing them as treatments for people with CJD. Although CJD is not common, studying rare disorders often has broader public health implications. Although the mechanisms and proteins are not the same as for prions, the theme of abnormal protein aggregation is a common factor in several neurological diseases, so similar drug strategies may be more widely applicable. Another general trend illustrated here is that drugs used for one purpose may find important uses for other disorders. NIH, working together with private disease advocacy groups, is currently sponsoring a program for screening FDA approved compounds for other neurodegenerative diseases.

Korth C, May BCH, Cohen FE, and Prusiner SB: Acridine and phenothiazine derivatives as pharmacotherapeutics for prion disease. Proceedings of the National Academy of Sciences USA 98: 9836-9841, 2001.

Chronic Lyme Disease Symptoms Not Improved by Intensive Antibiotic Treatment

Background: Lyme disease, an infection caused by the bacterium *Borrelia burgdorferi*, is transmitted to people by deer ticks and western black-legged ticks. The number of Lyme disease cases reported annually in the U.S. has increased 25-fold since national surveillance began in 1982. About 15,000 cases of Lyme disease are reported each year, making it the leading cause of vector-borne infectious illness in this country. In its early stages, Lyme disease usually can be treated successfully with standard oral antibiotics. If left untreated or inadequately treated, the infection can progress to late-stage complications requiring more intensive antibiotic therapy. In some patients, however, symptoms persist after the completion of the recommended treatment. Although some physicians prescribe long-term antibiotic regimens for these patients, the effectiveness of this approach has been controversial.

Advance: Data from two clinical trials provide evidence that intensive antibiotic therapy is not more effective than placebo in improving chronic Lyme disease symptoms. Study volunteers received standard antibiotic treatment for Lyme disease but suffered from persisting physical and cognitive problems related to their illness including muscle or joint pain and memory and concentration problems, often associated with fatigue. Researchers assigned volunteers at random to receive either antibiotic treatment or a placebo. The study compared treatment with 30 days of intravenous ceftriaxone followed by 60 days of oral doxycycline to treatment with intravenous placebo followed by oral placebo for the same duration. Researchers evaluated symptom improvement based on patients' responses to a health-related quality of life questionnaire given 90 days after completion of the antibiotic or placebo regimen. Analysis of the responses showed no significant difference in the percentage of patients who felt their symptoms had improved, worsened, or stayed the same between the antibiotic treatment and the placebo group. Investigators also found that the impact of chronic Lyme disease on physical health was at least equal to the disability of patients with congestive heart failure or osteoarthritis. In addition, investigators found no evidence of the Lyme disease bacterium in blood or spinal fluid from patients with chronic symptoms.

Implications: These findings, coupled with the knowledge of treatment of other chronic infectious diseases caused by persistent bacteria, suggest that it is unlikely that a longer course of antibiotic therapy or different antibiotic combinations would further improve chronic symptoms. Thus, patients can be spared a costly, ineffective treatment associated with side effects. Researchers will characterize the patients in the studies as thoroughly as possible to learn more about the mechanisms involved in chronic Lyme disease. The role that autoimmune reactions (immune system reactions against the body's own tissues) may play in persistent symptoms is also under investigation. Knowledge gained from these continuing studies could lead to more effective approaches for treatment of chronic Lyme disease.

Klempner MS, Hu LT, Evans J, Schmid CH, Johnson GM, Trevino RP, Norton D, Levy L, Wall D, McCall J, Kosinski M, and Weinstein A: Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. The New England Journal of Medicine 345: 85-92, 2001.

New Compound Blocks Marijuana's High

Background: Marijuana is the most widely abused illicit drug. Currently over 100,000 marijuana users seek treatment for their marijuana addiction, and data from the National Comorbidity Survey suggest that approximately 6 million people have had problems with marijuana dependence at some point in their life. Neurobiological studies have discovered that _-9-tetrahydrocannabinol (THC), the primary psychoactive ingredient in marijuana, acts at two receptor subtypes to produce its many effects. THC produces its behavioral, cardiovascular, analgesic, psychomotor, and cognitive effects through interactions primarily with the CB1 cannabinoid receptor. The elucidation of the role of the CB1 cannabinoid receptor is leading scientists to develop new compounds that can selectively block many of marijuana's effects.

Advance: A new compound, SR141716, that blocks the ability of THC to recognize the CB1 receptor, was tested for its ability to block marijuana's behavioral and cardiovascular effects in healthy men with a history of marijuana use. In a randomized, placebo controlled, double-blind study, increasing doses of SR141716 were found to attenuate the acute psychological and physiological effects of smoked marijuana. The 90 mg dose of SR141716 (the highest dose tested) produced an almost 50 percent reduction compared to placebo controls in the high produced by a smoked marijuana cigarette. An almost 60 percent reduction in heart rate was also found. SR141716 also appears to be a safe medication in that it produced no significant physiological or behavioral effects and was well tolerated by the subjects.

Implications: Not only does SR141716 appear to be a promising therapeutic agent for marijuana addiction, the findings of this study have significant implications for understanding the neurobiology of the endogenous cannabinoid system and its role in other clinical disorders. Animal studies have shown that compounds that activate the CB1 receptor impair learning and memory and increase appetite and food intake. The cannabinoid system may also play a role in psychotic disorders with the recent finding of increased concentrations of anandamide, a naturally occurring brain chemical that acts at the cannabinoid receptors, in the cerebrospinal fluid of schizophrenic patients. Further research into the role of CB1 receptors and the pharmacology of marijuana may lead to improved treatment for disorders related to dysfunction of the endogenous cannabinoid system and to the development of novel therapeutic agents.

Huestis MA, Gorelick DA, Heishman SJ, Preston KL, Nelson RA, Moolchan ET, and Frank RA: Blockade of effects of smoked marijuana by the CB1-selective cannabinoid receptor antagonist SR141716. Archives of General Psychiatry 58: 322-328, 2001.

Reducing Women's Concern About Weight Gain Improves Smoking Cessation Rates

Background: Stopping smoking is rarely easy. Research shows that it is often more difficult for women to quit than it is for men. One of the reasons for this is that women may be more concerned about the weight gain that often accompanies a quit attempt than men. Research confirms that women do in fact gain more weight than men after quitting smoking. Because concerns about weight gain have been recognized as a significant obstacle to smoking cessation, several clinical trials have evaluated the efficacy of adding a diet and exercise component to standard smoking cessation programs. The results were not very encouraging. Researchers thought the optimal strategy for treating weight-concerned women smokers may be to refrain from focusing on weight-related issues during smoking cessation, so that participants can devote their full efforts to following cessation counseling advice during and after the quit attempt.

Advance: Researchers found that treatment for addiction to nicotine that focused on reducing concerns about weight gain can significantly improve smoking cessation in women. Investigators randomly assigned 219 women smokers who wanted to stop smoking, but were worried about gaining weight, to one of three smoking cessation groups. One group received standard smoking cessation therapy, where weight gain was not explicitly addressed. Another received the same smoking cessation program plus diet advice. The third group received the standard program plus cognitive behavioral therapy to reduce concern about gaining weight, but dieting was discouraged. One year after treatment, 21 percent of the women who received the third therapy, which was the smoking cessation program plus cognitive therapy to reduce concerns about weight gain, had completely quit smoking (with no relapses), compared to 13 percent of the group that was dieting, and 9 percent of the standard therapy group. Surprisingly, the women in the group receiving cognitive therapy to alleviate weight gain concerns fared best in terms of preventing weight gain. One year after treatment they gained less than the other two groups. On average, they gained about 5.5 pounds, whereas women in the dieting group and the standard therapy groups gained 11.9 pounds and 16.9 pounds, respectively.

Implications: This study indicates that directly reducing the concerns about weight and promoting the acceptance of modest weight gain, by focusing on the health benefits of quitting smoking and improving body image, helps weight-concerned women stop smoking. Combining cognitive behavioral interventions with standard smoking cessation programs may be the most effective ways to reduce smoking in weight-concerned smokers. This may substantially improve the poor cessation rates in the subgroup of weight-concerned smokers.

Perkins KA, Marcus MD, Levine MD, D'Amico D, Miller A, Broge M, Ashcom J, and Shiffman S: Cognitive-behavioral therapy to reduce weight gain concerns improves smoking cessation outcome in weight-concerned women. Journal of Consulting and Clinical Psychology (in press 2001).

Addiction Treatment Programs Specifically Tailored to Adolescents Can Be Effective in Reducing Drug Use, Criminal Activity, and Improving School Performance

Background: We know very little about how best to treat adolescents and teens with drug abuse problems. In many cases, treatment programs are not specifically tailored to meet the changing developmental needs of this population. To determine if adolescent treatment programs offered in four major cities were showing positive outcomes after treatment was completed (reduced drug use, reduced criminal activity, improved school performance), NIH-supported researchers designed the Drug Abuse Treatment Outcome Studies for Adolescents (DATOS-A).

Advance: DATOS-A is the first large-scale study to evaluate treatment outcomes for adolescents. The basic conclusion from the two-year study is that when comparisons were made between the year prior to enrollment to treatment to a year following treatment, significant improvements were made in drug and alcohol use, school performance, and criminal activity. Weekly or frequent marijuana use dropped from about 80 percent to just over 43 percent. Heavy drinking dropped from nearly 34 percent to 20 percent, and criminal activities dropped from just over 75 percent to about 53 percent. Attendance and performance in school also improved following treatment. The researchers also concluded that similar to adult populations, the longer an individual stays in treatment the better the outcomes. This particular study included 1,167 adolescents who ranged in age from 11 to 18. The 368 females and 799 male participants were from and enrolled in treatment programs in Pittsburgh, PA; Minneapolis, MN; Chicago, IL; and Portland, OR. They were in one of three types of treatment: residential, out-patient drug-free programs, or a short-term inpatient program.

Implications: Given the increasing number of adolescents who reportedly use drugs, it is imperative that we have in place effective treatment programs that are specifically tailored to the developmental needs of this population. This research implies that community-based treatment programs can reduce drug and alcohol use, improve school performance, and lower involvement with the criminal justice system. Now researchers need to devise strategies specific to adolescents that can help improve the retention and completion rates.

Hser Y, Grella CE, Hubbard RL, Hsieh S, Fletcher BW, Brown BS, and Anglin D: An evaluation of drug treatments for adolescents in 4 US cities. Archives of General Psychiatry 58: 689-695. 2001.

Treating African-Americans with Kidney Disease Due to High Blood Pressure

Background: Mortality in the U.S. from disease of the blood vessels due to high blood pressure, or hypertension, has declined progressively over the past two decades, ascribed in part to improved treatment of high blood pressure (BP). However, during the same period, the incidence of kidney failure due to hypertension has increased steadily, particularly among African-Americans. In certain age groups, the risk of hypertensive kidney failure for African-Americans is 20 times greater than in whites. The optimal strategy for treatment of hypertension to prevent kidney failure, especially among African-Americans, has remained elusive. Recent studies on diabetic and nondiabetic kidney disease associated with excretion of protein into the urine have suggested significant benefits of treatment with drugs known as angiotensin-converting enzyme inhibitors (ACEIs) and calcium channel blockers (CCBs). Nevertheless, the impact of these drugs on the progression of kidney disease in African-Americans is unknown since all published trials had too few African-American participants. The African-American Study of Kidney Disease and Hypertension (AASK) was designed to evaluate the impact on progression of hypertensive kidney disease of three drugs belonging to different antihypertensive drug classes: metoprolol, amlodipine, and ramipril. To date, AASK is the largest comparative drug intervention trial that has focused on hypertensive kidney disease conducted in any population and the first clinical trial with a sufficient number of participants to evaluate the effect of the treatments in African-Americans. Recruitment into the full-scale trial began in February 1995, with planned follow-up through September 2001.

Advance: Investigators from the Morehouse School of Medicine and Charles R. Drew University participated in this comparison of the effects of the three drugs on hypertensive kidney disease progression. In September 2000, the amlodipine part of the study was terminated because of safety concerns. However, both the ramipril versus metoprolol comparison and the comparison of low versus high blood pressure groups will continue until the scheduled end of the study. Since the study investigators must remain blinded to the ongoing ramipril versus metoprolol study and low versus high blood pressure comparisons, the initial findings compare only amlodipine and ramipril. The study found that among participants with protein in their urine the ramipril group compared with the amlodipine group had a 38-percent reduced risk of decreased kidney function and a slower disease progression.

Implications: Ramipril, compared with amlodipine, retards kidney disease progression in African-American patients with hypertensive kidney disease and protein in the urine and may offer benefit to African-American patients without protein in the urine.

Agodoa LY, Appel L, Bakris GL, Beck G, Bourgoignie J, Briggs JP, Charleston J, Cheek D, Cleveland W, Douglas JG, Douglas M, Dowie D, Faulkner M, Gabriel A, Gassman J, Greene T, Hall Y, Hebert L, Hiremath L, Jamerson K, Johnson CJ, Kopple J, Kusek J, Lash J, Lea J, Lewis JB, Lipkowitz M, Massry S, Middleton J, Miller ER, Norris K, O'Connor D, Ojo A, Phillips RA, Pogue V, Rahman M, Randall OS, Rostand S, Schulman G, Smith W, Thornel-Brown D, Tisher CC, Toto RD, Wright JTJr, and XU S: Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. The Journal of the American Medical Association 285: 2719-2728, 2001.

Structural Insight into Improving Cholesterol-Reducing Medicines

Background: Elevated cholesterol levels are a primary risk factor for coronary artery disease. This disease is a major problem in developed countries and currently affects 13 to 14 million adults in the U.S. alone, according to the American Heart Association. But cholesterol is also an essential component of the body's biochemical inventory because it is the starting material for the synthesis of many hormones. Under normal conditions, our bodies produce about two-thirds of the needed cholesterol; the rest is obtained in the diet. The enzyme HMG-CoA reductase (HMGR), which performs a key step in cholesterol biosynthesis, can be blocked with drugs called statins that bind very tightly to the enzyme, prevent its activity, and effectively lower blood cholesterol levels. These inhibitors are widely prescribed medicines in the treatment of high blood cholesterol. Efforts to further improve these medicines or develop new ones will be greatly facilitated by knowledge of the molecular interactions between the enzyme and the inhibitors.

Advance: The three-dimensional molecular structures of the active portion of human HMGR complexed with six different statins were determined using x-ray crystallography. Part of the data collection for this project was done using the brilliant x-ray beam produced at the NIH-supported Macromolecular Diffraction Facility at the Cornell High Energy Synchrotron Source (CHESS). All the statins have a similar component in common, to which different, bulky chemical groups are attached. The results show that for all HMGR-statin complexes, the statin binds to the enzyme at the same location as the natural substrate. The bulky group on the statin is then positioned to make contact with the enzyme in such a way that the shape of the enzyme is disordered. This mode of binding has two effects: the statin occupies the active site and thus prevents binding of the natural cholesterol precursor substrate, and it prevents the complete formation of the active site, rendering the enzyme inactive.

Implications: The enzymatic activity of HMGR is heavily regulated by control mechanisms in the body to keep the concentration of cholesterol within acceptable limits. Because of its central role in cholesterol synthesis, HMGR is an ideal drug target if blood cholesterol levels need to be reduced. Administering statins has a profound effect in most patients. Although the statins that are currently available or in late-stage pharmaceutical development excel in curtailing the biosynthesis of cholesterol, visualization of statins bound to HMGR will assist chemists in their attempts to develop even better medicines to lower cholesterol levels.

Istvan ES, and Deisenhofer J: Structural mechanism for statin inhibition of HMG-CoA reductase. Science 292: 1160-1164, 2001.

Coagulation Factor VIII Gene Transfer in Severe Hemophilia A

Background: Hemophilia is an inherited bleeding disorder resulting from low or absent levels of any of a number of blood clotting factors. In the severe form of hemophilia due to factor VIII deficiency, bleeding into joints, soft tissues, and vital organs can occur spontaneously. The primary treatment has been replacement with factor VIII, which is concentrated from human blood products or genetically engineered. Either product requires frequent administration, and the former has led to complications from serious blood-borne infections (including AIDS) and the latter products are in short supply. Hemophilia is a particularly attractive candidate for gene therapy for several reasons. Even low levels of the factor are beneficial, the chance of an overdose is slight, and there is no requirement for production of the factor by a specific organ. Early attempts to develop treatments for this type of hemophilia with gene therapy were unsuccessful because of insufficient transfer of the gene to cells and production of too low amounts of the factor.

Advance: Investigators developed a gene-delivery system, wherein stable factor VIII genes were introduced into cultures of skin cells derived from the patients. These cells were then injected into the abdominal cavity of the patients. In four of the six patients receiving this therapy, factor VIII levels increased over baseline and this increase correlated with improvements in clinical measures of bleeding and need for additional administered factor. Also, there were no serious adverse events and no development of inhibitors against the clotting factor, even after two years of follow-up. In one patient, the beneficial effects lasted 10 months.

Implications: The implications of this study are far-reaching. Continued success with this model of gene therapy for factor VIII deficiency shows promise for a valuable treatment option in this population of hemophiliacs. More importantly, this approach may be applicable to treatment of hemophiliacs with deficiencies in other clotting factors.

Roth DA, Tawa NE, O'Brien JM, Treco DA, Selden RF, and Factor VIII Transkaryotic Therapy Study Group: Nonviral transfer of the gene encoding coagulation factor VIII in patients with severe hemophilia A. The New England Journal of Medicine 344: 1735-1742, 2001.

Candidate Drug for Treatment of Lupus

Background: In the disease systemic lupus erythematosus (SLE), there is an abnormal imbalance in certain types of T lymphocytes, causing increased production of a cell surface-associated compound known as CD154 and overproduction of an immunoregulatory substance called interleukin-10. At the same time, there is not enough produced of the important compound interferon-gamma, which is a basic component of the immune system. These abnormalities of the immune system lead to the production of autoantibodies – antibodies that harm the body in which they are produced – and the irreversible organ failure associated with SLE.

Advance: In this study, partly conducted at the General Clinical Research Center at Wake Forest University, researchers studied the effects of the drug trichostatin A, an inhibitor of an enzyme involved in modification of proteins called histones, on lymphocytes from lupus patients. Trichostatin A significantly reduced expression of CD154 and IL-10 and increased the expression of IFN-gamma in the lupus T cells.

Implications: Trichostatin A can simultaneously reverse the skewed expression of multiple genes implicated in the immunopathogenesis of SLE. This pharmacologic agent may be a candidate for the treatment of this autoimmune disease.

Mishra N, Brown DR, Olorenshaw IM, and Kammer GM: Trichostatin A reverses skewed expression of CD154, interleukin-10, and interferon-gamma gene and protein expression in lupus T cells. Proceedings of the National Academy of Sciences USA 98: 2628-2633, 2001.

Recovery of Breathing Function in Spinal Cord Injured Patients

Background: About 183,000 to 230,000 people live daily with the traumatic consequences of spinal cord injury in the U.S., with 10,000 more new cases added annually. A major life-threatening consequence of high cervical spinal cord injury is the interruption of respiratory pathways, which leads to partial paralysis of the diaphragm muscle and respiratory distress. Currently, mechanical ventilators provide the primary means of treating spinal cord-injured patients who cannot breathe on their own. However, this kind of therapy leads to a tremendous sense of isolation and loss of independence.

Advance: NIH-supported scientists who examine recovery of breathing function are widely recognized for their pioneering work on respiratory muscle paralysis after cervical spinal cord injury. They demonstrated that alternative respiratory motor pathways can be activated upon spinal injury. This process, known as "crossed phrenic phenomenon," was first shown to exist in a rodent model of spinal injury. Specifically, damage to the spinal column that affects the phrenic (or diaphragm) nerve results in the inability to breathe, which then intensifies the central respiratory function and eventually triggers an inactive pathway of respiratory nerve cells parallel to those that were damaged. Findings from the initial studies of these alternative pathways, and the nervous system's ability to use them in response to injury, suggested that certain treatments may enhance and speed the activation of this crucial pathway to the diaphragm muscle. The scientists have now demonstrated in the rodent model that using the drug, theophylline, significantly increases the speed at which the brainstem re-establishes communication with the diaphragm after spinal cord injury. Currently, the scientists are extending this dramatic finding to explore the feasibility of using theophylline to treat and enhance breathing in humans.

Implications: Breathing dysfunction is the leading cause of death in humans in the first year after spinal cord injury. The development of a drug therapy that enhances breathing in people with high cervical spinal cord injury could greatly improve their chances of survival and enhance their independence and quality of life.

Nantwi KD and Goshgarian HG: Alkylxanthine-induced recovery of respiratory function following cervical spinal cord injury in adult rats. Experimental Neurology 168: 123-134, 2001.

Phillis JW and Goshgarian HG: Adenosine and Neurotrauma: therapeutic perspectives. Neurological Research 23: 183-189, 2001.

Testosterone Protects Against the Cancer-Causing Effects of Estrogen on Breast Tissue

Background: Breast cancer is estimated to affect 1 in 8 women during their lifetime. Despite recent advances in treatment that have increased the survival rate of women diagnosed with breast cancer, the disease remains the most common form of cancer affecting women. It is now well established that estrogens, which are produced mainly by the ovaries, are the most significant risk factor for breast cancer: the longer breast tissue is exposed to estrogen, the higher the risk. Estrogen production reaches its peak levels during puberty. Thus, the earlier a woman starts to menstruate, the higher her risk of developing breast cancer, and the later she experiences menopause, the higher the risk. There is also concern that hormone replacement therapy (HRT) with estrogen, which helps to alleviate the symptoms of menopause, is placing older women at increased risk for breast cancer.

Estrogen, however, is not the only hormone to influence the growth of breast tissue. Clinicians have known for some time that androgens, or male sex hormones, also play a critical role in breast development. For instance, in certain disorders of the adrenal gland, in which there are higher than normal levels of androgens, the breast tissue of female patients is underdeveloped. By contrast, in an inherited disorder known as testicular feminizing syndrome, males have very large breasts. In these patients, the androgen receptor (the cell surface molecule that picks up circulating androgens and ferries them into the cell) is defective, so that androgens are rendered inactive. These findings have led researchers to hypothesize that normal breast growth is the result of a balance between the positive effects of the female sex hormones and the negative effects of the male sex hormones.

Advance: NIH investigators conducting HRT research in primates have found that while estrogen causes breast tissue to grow, the male hormone testosterone significantly curtails the growth-promoting effects of estrogen. Furthermore, researchers found that drugs which block the action of testosterone cause massive proliferation of breast tissue.

Implications: These observations suggest that combined estrogen/androgen hormone replacement therapy might reduce the risk of breast cancer associated with estrogen replacement. Based on these findings, researchers are conducting clinical trials in two populations of young women who require HRT to counteract decreased estrogen levels: women with premature ovarian failure and women with Turner syndrome. These trials are very new and constitute the first controlled studies to combine testosterone with estrogen replacement in women with ovarian failure. Although these studies will be too short in duration (2-3 years) and have too few subjects to determine conclusively if breast cancer risk can be reduced, researchers hope that the treatment will reduce estrogen's stimulation of breast tissue, and also provide other benefits, such as increasing bone and muscle strength and sexual function in these patients.

Zhou J, Ng S, Adesanya-Famuiya O, Anderson K, and Bondy CA: Testosterone inhibits estrogen-induced mammary epithelial proliferation and suppresses estrogen receptor expression. Federation of American Societies for Experimental Biology 14: 1725-1730, 2000.

New Treatment Increases Chances for Pregnancy in Women With Polycystic Ovary Syndrome

Background: Polycystic Ovary Syndrome (PCOS), a common endocrine disorder that affects as many as 5 million premenopausal women, is the most common cause of female infertility in the U.S. The features of PCOS may vary, but they often include failure to ovulate or to menstruate. However, PCOS is more than just a reproductive disorder, it is a major health concern for women who are affected. Many women with PCOS are also obese, have high blood pressure, hardening of the arteries, and abnormal fat metabolism, all of which can lead to heart disease. In addition, these women often cannot use insulin properly and have elevated levels of insulin in their blood. Interestingly, these obese women also do not respond to clomiphene citrate (CC), the primary therapy used to induce ovulation in women with PCOS.

Advance: NIH-supported researchers recently demonstrated that by using the drug metformin, which restores the body's ability to use insulin effectively, they also could increase the ovulation and fertility rates in women with PCOS. Of 12 women given metformin, along with treatment to induce ovulation, 9 ovulated (75 percent) and 6 conceived. In contrast, of the 15 women given CC alone, ovulation occurred in only 4 (27 percent) and conception in 1.

Implications: The dramatic results show that a combination of metformin with CC therapy can increase the chances of ovulating and of becoming pregnant in obese women with PCOS. This offers new hope to this group of women who previously had been generally unsuccessful with infertility treatment. In addition, this new treatment holds promise for reducing health care expenditures by providing an alternative to such costly infertility treatments as using gonadotropins to induce ovulation, or using a variety of *in vitro* fertilization-embryo transfer procedures. Furthermore, inducing ovulation with CC and metformin has the advantage of lowering the occurrence of multiple pregnancies and ovarian hyperstimulation syndrome. Not only can this reduce costs but it can potentially have positive health implications for both the mother and her offspring.

Vandermolen DT, Ratts VS, Evans WS, Stovall DW, Kauma SW, and Nestler JE: Metformin increases the ovulatory rate and pregnancy rate from clomiphene citrate in patients with polycystic ovary syndrome who are resistant to clomiphene citrate alone. Fertility and Sterility 75: 310-315, 2001.

Tubal Sterilization Does Not Increase the Risk of Menstrual Abnormalities

Background: Tubal sterilization, commonly known as tubal ligation, is used by more women in the U.S. than any other single method of contraception. Although it is a very safe and effective procedure, questions have been raised for decades as to whether the procedure causes menstrual abnormalities. To address this issue, scientists from the NIH-supported U.S. Collaborative Review of Sterilization (CREST), compared the likelihood of persistent menstrual abnormalities among women who had undergone tubal sterilization to those among women who had not undergone the procedure. In a multicenter, prospective, 5-year, cohort study, CREST followed 9,614 women who underwent the procedure for tubal sterilization and 573 women whose partners underwent vasectomy, in lieu of tubal sterilization, as their birth control method of choice.

Advance: The women who had undergone sterilization were no more likely than those who had not undergone the procedure to report persistent changes in between-cycle bleeding or in the length of the menstrual cycle. Compared to the women who were not sterilized, women who had undergone tubal sterilization were more likely to report fewer days of bleeding, less severe bleeding, and less menstrual pain. The sterilized women were more likely to report having irregularly occurring periods; however, because the results reported in previous research were inconsistent with this finding and there are no known biologic hypotheses for it, the researchers attributed this finding to chance.

Implications: This large, comprehensive study provides the best evidence to date that women who have undergone tubal sterilization are no more likely than other women to have menstrual abnormalities. The findings are important because they settle the longstanding debate within the medical community and put to rest any lingering doubts about the safety of tubal ligation. The findings also reassure the millions of women worldwide who have already undergone tubal sterilization and provide important information for women considering to use this method of fertility control, as well as for health care providers who must counsel them. But perhaps most important are the potential public health ramifications of the study. One of the highest rates of unplanned pregnancy occurs among women aged 40 years or older. Reassuring women in their later reproductive years that tubal ligation is safe provides these women with an effective means to prevent an unplanned pregnancy.

Peterson HB, Jeng G, Folger SG, Hillis SA, Marchbanks PA, and Wilcox LS: The risk of menstrual abnormalities after tubal sterilization. The New England Journal of Medicine 343: 1681-1687, 2000.

Low-Cost Supplement is Effective in Improving Child Health in Developing Countries

Background: In developing countries, seven out of ten childhood deaths can be attributed to pneumonia, diarrhea, measles, malaria, and malnutrition. The prevalence of these illnesses is often due to impaired functioning of the immune system that results from environmental factors common to the developing world, including chronic malnutrition. Zinc deficiency, in particular, is common among children in these countries. This nutrient normalizes cell functions in many different tissues and increases the number of white blood cells available to fight infection.

Advance: Findings from previous clinical studies document the effects of zinc supplementation on malnourished infants and young children in various developing countries. The scientists found that such supplementation decreases the incidence of diarrhea and dysentery by as much as 27 percent; and decreases the incidence of pneumonia, by 41 percent. Most recently, NIH-supported scientists pooled and analyzed these various studies to determine what additional effects zinc supplementation can have if it is used simultaneously with oral rehydration therapy, a common treatment for diarrhea. The scientists found that children who received both treatments had a 42 percent lower rate of treatment failure or death compared to children who received only oral hydration therapy.

Implications: This study demonstrates how the cost-effective pooling of data from previous clinical studies can identify and strengthen the scientific evidence base for new or improved treatment practices. In this case, the research findings strongly confirmed the value of using a *low-cost* supplement such as zinc, in addition to conventional treatments, to further improve immune system function and, more importantly, survival rates of children who suffer from diarrhea in developing countries. The data provide the evidence that this simple and low-cost combination of approaches should become a new standard of treatment that can save the lives of some of the world's most vulnerable children.

Bhutta ZA, Bird SM, Black RE, Brown KH, Gardner JM, Hidayat A, Khatun F, Martorell R, Ninh NX, Penny ME, Rosado JL, Roy SK, Ruel M, Sazawal S, and Shankar A: Therapeutic effects of oral zinc in acute and persistent diarrhea in children in developing countries: pooled analysis of randomized controlled trials. American Journal of Clinical Nutrition 72: 1516-1522, 2000.

Androgen Blockers Can Help Women With Infertility Caused by Polycystic Ovary Syndrome

Background: Polycystic Ovary Syndrome (PCOS) is a complex disorder that affects 5-10 percent of women in their childbearing years. PCOS is the most common cause of infertility, as many of these women fail to ovulate or menstruate. Normally, ovulation is controlled by the rise and fall of opposing hormones within a woman's body. For example, androgens, or male hormones, suppress ovulation while the female hormones, estrogen and progesterone, stimulate ovulation. Previously, researchers showed that women with PCOS had higher levels of androgens. The androgens stimulate the secretion of luteinizing hormone (LH), which represses ovulation. LH levels rise in response to signals from LH-releasing hormone (LHRH). In normal circumstances, estrogen and progesterone inhibit LHRH release, which causes LH to decrease and ovulation to occur. However, women with PCOS do not show this normal inhibition of LHRH, and have increased levels of LH.

Advance: To follow up on these findings, NIH-sponsored researchers studied whether the elevated androgen levels exhibited in PCOS could be responsible for blocking the action of estrogen and progesterone and thereby inhibiting ovulation. The scientists treated ten non-ovulating women who had PCOS with an androgen blocking drug, flutamide, in addition to using the standard treatment of estrogen and progesterone supplements. These women were compared to a similar group of controls who received only the standard treatment. The LH levels of women who received estrogen and progesterone alone were not reduced; however, when an androgen blocker was added, LH levels decreased.

Implications: The findings suggest that administering an androgen-blocking drug can restore the normal response to estrogen and progesterone in adult women with PCOS. Moreover, the study demonstrates that reducing excess androgen secretion or blocking androgen action is important in restoring normal ovarian regulation of LHRH and LH secretion. Together, the research holds promise for a range of novel treatments to restore regular ovulation, and hopefully fertility in women with PCOS.

Eagleson CA, Gingrich MB, Pastor CL, Arora TK, Burt CM, Evans WS and Marshall JC: Polycystic ovarian syndrome: evidence that flutamide restores sensitivity of the gonadotropin-releasing hormone pulse generator to inhibition by estradiol and progesterone. Journal of Clinical Endocrinology and Metabolism 85: 4047-4052, 2000.

Study Suggests Lumpectomy is at Least as Cost-Effective as Mastectomy When Long-Term Medical Care Costs Are Considered

Background: Breast-conserving therapy (BCT) for early-stage breast cancer – sometimes referred to as "lumpectomy"– was endorsed by a NIH consensus conference in 1990 after randomized trials showed it to be equal in effectiveness to the prior standard of care, mastectomy. Subsequent studies confirmed this finding. Nevertheless, mastectomy remains popular, although there is widespread geographic variation in its use. Factors that influence a woman's choice between BCT and mastectomy include the size and stage of the cancer, the woman's age, and whether the woman has other illnesses. Another factor that may affect treatment choice is the cost of BCT versus mastectomy. Although shorter hospital stays and fewer complications are associated with BCT, this therapy typically requires additional radiation treatment. Three previous studies suggested that BCT was more expensive than mastectomy because of these additional radiation treatments. However, these studies did not consider long-term costs. Due to the limitations of these and other previous studies, it remained unclear whether BCT, while equal to mastectomy in effectiveness, was more costly.

Advance: A new study by NIH-supported researchers suggests that when long-term costs – up to 5 years after diagnosis – are taken into consideration, there is little difference in costs between BCT and mastectomy. The researchers compared the costs of all medical care for 1,675 women aged 35 and older with early-stage breast cancers treated by either BCT or mastectomy between 1990 and 1998. Monthly costs were analyzed by treatment method and adjusted for age and cancer stage. At 6 months after diagnosis, BCT was more expensive than mastectomy. At 1 year, the two treatment methods were equivalent in cost. By 5 years after diagnosis, however, medical costs of care were lower for women treated with BCT and radiation than for women treated with mastectomy. Treatment costs were higher for women under age 65 than for older women. An analysis of survival did not show a statistically significant difference by treatment method; therefore, the long-term difference in costs cannot be explained by a difference in survival between women treated with BCT versus those treated with mastectomy. A strength of the study is that the results are based on a large population-based sample of all early-stage breast cancers followed comprehensively for up to 5 years after diagnosis. However, the study considered only medical care costs and did not include other economic measures such as lost work time by the patient or members of her family. The study was conducted at Group Health Cooperative, a large, regional nonprofit health maintenance organization in Washington state.

Implications: These results suggest that BCT is at least as cost-effective as mastectomy and should be weighed equally in treatment considerations about cost. Because survival rates after the two therapies are similar, a woman's choice of treatment should be driven by the characteristics of her tumor, her medical condition, her physician's counseling, and her own evaluation of her options. The larger lesson learned from this study is that the short-term and long-term treatment costs may be quite different. Health care policy decisions should be based on data about both long-and short-term costs.

Barlow WE, Taplin SH, Yoshida CK, Buist DS, Seger D, and Brown M: Cost comparison of mastectomy vs. breast-conserving therapy for early stage breast cancer. Journal of the National Cancer Institute 93: 447-455, 2001.

Immunotoxin Yields Promising Results Against Hairy Cell Leukemia in Early Trial

Background: Every year about 700 Americans are diagnosed with hairy cell leukemia (HCL) , a rare, slow-growing cancer of white blood cells. The disease gets its name because, under a microscope, the affected cells have short, thin surface projections that look like hairs. About two percent of all leukemias are of the hairy cell type. Currently, standard treatment for HCL consists of chemotherapy with the drugs pentostatin or cladribine. Eighty-five percent of patients treated with these drugs experience complete remission, and 60 to 75 percent may remain disease-free for up to 8 years. However, these drugs cause suppression of infection-fighting white blood cells known as CD4 cells. Furthermore, at least 25 percent of patients develop resistance to these drugs and respond poorly to other therapies. About 15 percent of patients, who have high levels of hairy cells circulating in their blood, respond poorly to treatment with pentostatin and cladribine.

Advance: NIH researchers have developed a new treatment that, in an early trial, achieved complete remission in a high percentage of HCL patients who are resistant to chemotherapy with pentostatin and cladribine. Eleven of 16 patients had a complete remission and two had a partial remission when treated with the recombinant immunotoxin BL22. A recombinant immunotoxin is an antibody that has been genetically engineered to deliver a deadly toxin to tumors – in this case, hairy cell leukemia cells. Those achieving complete remission included three patients with high levels of hairy cells circulating in their blood. The patients who did not respond to BL22 were taking low doses of the immunotoxin or were resistant to the therapy because their own antibodies interfered with it. After about 1 to 2 years, three of the 11 patients who initially went into remission relapsed. When these patients were treated with BL22 again, however, they achieved remission once more. Two of the 16 patients developed a serious but reversible complication that can result in severe kidney damage. Both patients recovered, had complete remissions, and suffered no kidney damage. Following a modification in the method of BL22 administration, no further cases of this complication have occurred. Unlike pentostatin and cladribine, BL22 does not appear to harm CD4 cells. Patients can be treated multiple times because the treatment does not become toxic, and the immunotoxin continues to kill hairy cells. The trial also included some patients with other types of leukemia. Although the most dramatic response to BL22 was seen in HCL patients, patients with chronic lymphocytic leukemia – a more common cancer of white blood cells – also benefitted from treatment with the immunotoxin.

Implications: BL22 is the first treatment developed in more than 10 years to achieve complete remissions in the majority of HCL patients treated and the only treatment to achieve complete remissions in a majority of HCL patients in whom chemotherapy is ineffective. These results are particularly impressive because they occurred in a Phase I trial, an early trial designed primarily to determine how to administer a drug safely, not cure the disease. If the results are confirmed in further trials, they offer new hope to all HCL patients. It is also possible that BL22 will prove effective in treating other types of leukemia.

Kreitman RJ, Wilson WH, Bergeron K, Raggio M, Stetler-Stevenson , FitzGerald DJ, and Pastan I: High complete remission rate in chemotherapy-resistant classic or variant hairy cell leukemia induced by the anti-CD22 recombinant immunotoxin BL22. The New England Journal of Medicine 345: 241-247, 2001.

Treatment to Boost Immune Actions of Blood-producing Cells May Improve Breast Cancer Therapy

Background: One therapy for recalcitrant breast cancer is to treat the patient with high enough levels of chemotherapy that her cells for producing blood are suppressed. Normally, such a treatment would prove fatal, but physicians then transplant, or graft, back into her body her own previously harvested peripheral blood stem cells that are capable of forming colonies and reconstituting her blood-producing system. The entire treatment is drastic and far from universally effective; sometimes, it keeps cancer at bay, and sometimes the patient relapses. To make it more productive, scientists have added interleukin-2.

In the normal body, when certain immune cells are triggered by a threat, they release interleukin-2. That triggers a chain reaction stimulating those same cells to reproduce thousands more like them, all armed to fight the invader. Scientists found that, if they incubated blood-producing stem cells in interleukin-2, they could produce "armed" immune cells. In laboratory tests, they found that these armed cells were more toxic to tumor cells than were untreated cells. Then, they infused these treated cells back into the breast cancer patient as part of her therapy, and the graft of the blood-producing cells "took" as well as if the cells had been untreated. Although toxicities to therapy were common with such a treatment regimen, the interleukin-2-incubated cells were shown to have stimulated the immune cells to attack remaining tumor cells – what researchers called a graft-versus-tumor effect.

Advance: In a Phase III study at several medical centers, researchers were able to show that therapy with the interleukin-2-incubated cells improved the survival of breast cancer patients over the standard therapy. The 59 patients in the study had high-risk breast cancer. After chemotherapy, 30 of them received the treated cells and 29 received untreated cells. Both groups continued to receive chemotherapy. Scientists found that toxicities for the two groups were the same, and the side effects were not permanent. Two years later, 76 percent of the treated-cell group and 51 percent of the untreated cell group were still free of cancer. Ninety-six percent of the treated cell group and 76 percent of the untreated cell group had survived.

Implications: Scientists found that incubating interleukin-2 with harvested blood-producing cells to stimulate them to attack the breast cancer tumor cells could significantly improve the efficacy of therapy for high-risk breast cancer, and improve length and quality of life for breast cancer survivors.

Meehan KR, Wu A, Hassan R, Miao Y, Chawla J, Slack R, Gehan E, and Herscowitz HB: Ex vivo cytokine activation of peripheral blood stem cells: a potential role for adoptive cellular immunotherapy. Journal of Hematotherapy and Stem Cell Research 10: 283-290, 2001.

Meehan KR, Arun B, Gehan EA, Berberian B, Sulica V, Areman EM, Mazumber A, and Lippman ME: Immunotherapy with interleukin-2 and alpha-interferon after IL-2-activated hematopoietic stem cell transplantation for breast cancer. Bone Marrow Transplant 23: 667-673, 1999.

Meehan KR, Verma UN, Cahill R, Frankel S, Areman EM, Sacher RA, Foelber R, Rajagopal C, Gehan EA, Lippman ME, and Mazumder A: Interleukin-2-activated hematopoietic stem cell transplantation for breast cancer: investigation of dose level with clinical correlates. Bone Marrow Transplant 20: 643-651, 1997.

Vaccine Made from Pancreatic Tumor Cells of Several People May Stimulate Immune System to Attack Pancreatic Cancer

Background: When people get the flu, their immune systems recognize the virus as an invader, attack it, and they recover. For reasons that are not yet clear, in persons who develop cancer the immune system does not recognize those cancer cells as a threat and does not attack them. For more than a decade, scientists searched for ways to "vaccinate" against a person's own cancer to stimulate the immune system to attack the cancer cells. Scientists were able to transfer certain genes into mouse tumor cells to cause them to produce large quantities of a particular protein named GM-CSF (for granulocytic-macrophage colony-stimulating factor). The GM-CSF stimulated the mouse immune system so that it attacked the mouse tumors. However, they found that in humans it is difficult to isolate enough of an individual's tumor cells and properly process them to produce sufficient GM-CSF. More recently, scientists were able to pool a mouse's own tumor cells with tumor cells from other mice, grow them in culture and genetically modify them to form a more easily produced "vaccine." This vaccine cured established tumors in mice but was not tried in humans.

Advance: Scientists tested the vaccine in patients with pancreatic cancer, a particularly vicious cancer with a 5-year survival rate of less than 5 percent. The scientists grew primary pancreatic tumor cells in cultures and then genetically modified them to produce GM-CSF. Fourteen patients received the vaccine eight weeks after pancreatic cancer surgery. Twelve of the patients also received a six-month course of radiation and chemotherapy. The survival rates were encouraging. The average length of survival of all pancreatic cancer patients who receive standard treatment – surgery, radiation, and chemotherapy – is six to nine months. The patients in the vaccine study survived disease-free for an average of 13 months. In the three patients with the highest dose, not only did their immune systems show a response, but they were alive and disease-free 25, 27, and 30 months after diagnosis. In addition, while a few patients had trouble with itching skin, the vaccine showed no serious toxic effects.

Implications: Scientists determined that the vaccine cells remained active in the person for a long enough time to be effective, and that the highest dose appeared safe and probably induced the immune system to attack the tumor. Phase II trials of the vaccine are underway to determine whether the promising effects will translate into medical benefits for a larger group of pancreatic cancer patients. This approach may work against a number of other types of cancer as well.

Jaffee EM, Hruban RH, Biedrzycki B, Laheru D, Schepers K, Sauter PR, Goemann M, Coleman J, Grochow L, Donehower RC, Lillemoe KD, O'Reilly S, Abrams RA, Pardoll DM, Cameron JL, and Yeo CJ: Novel allogeneic granulocyte-macrophage colony-stimulating factor-secreting tumor vaccine for pancreatic cancer: a phase I trial and immune activation. Journal of Clinical Oncology 19: 145-156, 2001.

Thomas MC, Greten TF, Pardoll DM, and Jaffee EM: Enhanced tumor protection by GM-CSF expression at the site of an allogeneic vaccine. Human Gene Therapy 9: 835-843, 1998.

Vaccines for Lung and Colon Cancer Show Promise

Background: Researchers all over the world are working to develop cancer vaccines. They have had success treating some malignancies this way, but not lung and colorectal cancers, which are the two most common cancers and the two leading causes of cancer deaths in the U.S. This year, NIH researchers discovered a new approach that showed promising clinical activity in a Phase I study.

Advance: First, the researchers isolated a new marker compound, or peptide, that is overexpressed in many cancers, including many of those that arise in the colon, pancreas, lung, and breast. They modified the peptide to make it more potent, then loaded it onto cells called dendritic (meaning branch-like) cells as a way to deliver the vaccine to the immune system T cells. It is rare to find dendritic cells in the blood, but these researchers found that treating advanced cancer patients with a growth factor increased dendritic cells in the body 20-fold. After vaccination, tumors in two of 12 patients with lung or colon cancer dramatically regressed, one patient's response was mixed, and two others had stable disease.

Implications: Only 12 patients have been treated, but the results are promising for a Phase I study. If more extended clinical trials show that the new approach is effective, it could lead to a vaccine for lung and colorectal cancer. For now, the researchers have provided insight and the basis for a new approach to vaccine strategies for these and other cancers.

Fong L, Hou Y, Rivas A, Benike C, Yuen A, Fisher GA, Davis MM, Engleman EG: Altered peptide ligand vaccination with Flt3L expanded dendritic cells for tumor immunotherapy. Proceedings of the National Academy of Sciences USA (in press 2001).

Vaccines for Melanoma Patients

Background: Melanoma is the fastest growing type of cancer in the U.S., and it is nearly always lethal once it spreads from its original location. There has been progress in developing effective immunotherapies for patients with metastatic melanoma. Using immune lymphocytes, a kind of white blood cell, from melanoma patients, researchers have identified and characterized genes that encode antigens, or marker compounds, that the immune system recognizes on melanomas. Identifying the genes that encode cancer antigens has made it possible to develop new therapies using active immunization – vaccines – against the antigens. Another approach is called cell-transfer therapy – transferring into patients immune cells that can recognize the tumor antigens.

Advance: NIH studies that involve immunizing, or vaccinating, metastatic melanoma patients against the melanoma antigen have helped researchers develop ways to raise immune cells in patients that can attack their own cancers. Immunizing patients with peptides from the antigens, along with interleukin-2 (IL-2) – a molecule that activates lymphocytes to attack tumor cells – has caused cancer regressions in one-third of all patients with metastatic melanoma. In pilot studies, tumor regressions are seen when combinations of peptides are used as vaccines without IL-2 or other immune cytokines. Recent studies have identified immune system killer cells and helper cells that are directed against cancer antigens. More cancer regressions are seen when these cells are grown in culture and transferred to cancer patients.

Implications: These studies are some of the first examples of successfully applying specific immunotherapy for human cancer based on a growing understanding at the molecular level of the immune response against cancer. Genes that encode antigens expressed on up to one-third of breast, ovarian, prostate, and lung cancers are now identified. Similar approaches are being applied to treatments for patients with these cancers.

Rosenberg, SA: Progress in human tumour immunology and immunotherapy. Nature 411: 380-384, 2001.

Rosenberg, SA: A new era in cancer immunotherapy based on the genes encoding cancer antigens. Immunity 10: 281-287, 1999.

Newman, J. "I have seen cancers disappear." Discover 45-50, 2001.

Beehive Product May Inhibit Dental Caries

Background: Propolis, a resinous product collected from beehives, has been used for thousands of years in folk medicine to treat wounds, ulcers, and diseases such as mouth and throat infections. Bees gather propolis from the buds of various poplar and conifer trees, mix it with beeswax and salivary secretions, and then use the substance to strengthen and protect their hive from germs and foreign invaders. Propolis also has antibacterial and antifungal effects that protect the bee colony against disease.

Advance: NIH-supported researchers have found that propolis significantly reduces dental plaque formation. Propolis is a potent inhibitor of glucosyltransferases (Gtf), enzymes that synthesize sticky glucans from table sugar (sucrose). Glucans promote the binding of cariogenic bacteria to teeth, which is a critical step in the development of dental decay. Investigators collected propolis from two different regions in Brazil and tested extracts of the substance both on purified Gtf enzymes in solution and on the surface of saliva-coated hydroxyapatite beads (designed to mimic the surface of a tooth). Propolis successfully inhibited 75-95 percent of Gtf activity in solution, and 45-95 percent of Gtf activity on the hydroxyapatite surfaces. Interestingly, the investigators discovered that the effectiveness of propolis depended on the geographic area from which it was collected. Among the Gtf enzymes tested were GtfB, GtfC, and GtfD, which are produced by *Streptococcus mutans*, the most common pathogen associated with dental caries. Of these, GtfB and GtfC appear to be the most important ones related to the development of dental plaque. Potential Gtf inhibitors tested in previous studies, including commercially available mouth rinses, have failed to significantly inhibit GtfC activity.

Implications: The current study demonstrates that propolis is a potent inhibitor of GtfC, whether the enzyme is exposed to the substance before or after adsorption to a surface. This level of inhibition has not been observed before. Further characterization of the structure and function of the active component of propolis may lead to a new anti-caries product.

Koo H, Smith AMV, Bowen WH, Rosalen PL, Cury JA, and Park YK: Effects of *Apis mellifera* propolis on the activities of Streptococcal Glucosyltransferases in solution and adsorbed onto the saliva-coated hydroxyapatite. Caries Research 34: 418-426, 2000.

Cellular Communication in Dental Plaque

Background: Dental plaque is made up of hundreds of species of bacterial cells. Most of these bacteria are harmless, and some may in fact be beneficial. But when harmful bacteria begin to displace 'good' bacteria, certain oral diseases, like periodontal (gum) disease can develop. The process that mediates this balance between 'good' and 'bad' bacteria is not well understood.

Advance: NIH-supported scientists have shed light on this process by demonstrating that oral bacteria talk to each other through chemical signals. They discovered that a 'good' bacterium, called *Streptococcus cristatus*, sends out a chemical signal to *Porphyromonas gingivalis,* a 'bad' bacterium which is implicated in adult periodontal disease. Upon sensing this signal, *P. gingivalis* stops the process of trying to stick to dental plaque.

Implications: If scientists could develop a method to encourage or amplify these chemical signals, harmful bacteria like *P. gingivalis* would be less able to adhere to dental plaque and would be more readily eliminated from the mouth. Capitalizing on this communication process could lead to new treatments for maintaining oral health and for preventing periodontal disease.

Xie H, Cook GS, Costerton JW, Bruce G, Rose TM, and Lamont, RJ: Intergeneric Communication in Dental Plaque Biofilms. Journal of Bacteriology 182: 7067-7069, 2000.

Fibrous Dysplasia of Bone

Background: Fibrous dysplasia of bone is a deforming and crippling skeletal disorder characterized by a softening and bending of bone caused by failure of bony tissue to calcify. McCune-Albright syndrome (MAS) is characterized by fibrous dysplasia as well as café au lait skin pigmentation and endocrine disorders, notably premature puberty. MAS is caused by mutations in the GNAS1 gene. Fibrous dysplasia also occurs in people who do not have MAS. While GNAS1 mutations have been found in individual patients with non-MAS fibrous dysplasia, it is not known if these mutations are common in such patients. A major problem in determining the frequency of mutation in non-MAS fibrous dysplasia patients is due to the mosaic nature of the disease resulting in varying ratios of normal to mutant cells, and lack of a sensitive technique.

Advance: NIH researchers and their collaborators looked for GNAS1 mutations in a group of eight consecutive non-MAS patients with fibrous dysplasia by developing a novel, highly sensitive technique. They identified the mutations in all eight patients. They also examined tissue from the patients, and found the same abnormalities seen in MAS. In addition, uncalcified bone matrix was a prominent feature of the patients' diseased bone. When stromal cells isolated from affected bone were transplanted into nude mice, the cells failed to make normal bone; instead, they formed a miniature replica of fibrous dysplasia.

Implications: This study provides evidence that GNAS1 mutations are common, if not universal, in non-MAS patients with fibrous dysplasia. Taken together, the study's findings suggest that fibrous dysplasia, MAS, and nonskeletal endocrine abnormalities associated with GNAS1 mutations represent a spectrum of manifestations of the same basic disorder. The researchers concluded that the same mechanisms underlie the development of bone lesions in MAS and non-MAS fibrous dysplasia. This suggests the possibility that when mechanism-targeted treatments are developed, they may work for both disorders.

Bianco P, Riminucci M, Majolagbe A, Kuznetsov SA, Collins MT, Mankani MH, Corsi A, Bone HG, Wientroub S, Spiegel AM, Fisher LW and Robey PG: Mutations of the GNAS1 gene, stromal cell dysfunction, and osteomalacic changes in non-McCune-Albright fibrous dysplasia of bone. Journal of Bone and Mineral Research 15: 120-128, 2000.

Novel Mechanism of Tumor Suppression in Oral Cancer Cells

Background: Ornithine decarboxylase (ODC) is an enzyme that is involved in cell proliferation and differentiation. Scientists believe that over-activity of ODC contributes to cancer development. Elevated levels of ODC have been reported in several cancers including those of the breast, stomach, and liver. Furthermore, over-activity of the enzyme has been shown to be an indicator of genetic change leading to oral cancer development. Inhibitors of ODC activity are believed to have potent anti-tumor effects. Ornithine decarboxylase antizyme (ODC-Az) is one such inhibitor that scientists believe may work by suppressing tumor growth.

Advance: NIH researchers have shown that ODC-Az can reverse malignancy in oral cancer cells and offer evidence of how the anti-enzyme works. In a laboratory study, the scientists inserted the ODC-Az gene into a hamster malignant oral cell line where it reversed the malignancy of the cells. Additionally, the scientists showed that ODC-Az suppressed tumor growth in an animal model. The data also revealed that the anti-enzyme worked by removing methyl sites from the cells' DNA, a reversal of hypermethylation – a process implicated in cancer development. The scientists speculate that removing methyl sites re-activates key cellular genes that can then suppress tumor growth.

Implication: Understanding how ODC-Az works may provide a basis for the development of potential new therapies based on this mechanism.

Tsuji T, Usui S, Aida T, Tachikawa T, Hu G-F, Sasaki A, Matsumura T, Todd R, and Wong DTW: Induction of epithelial differentiation and DNA demethylation in hamster malignant oral keratinocytes by ornithine decarboxylase antizyme. Oncogene 20: 24-33, 2001.

Potential Use of Human Dental Pulp Stem Cells in Tissue Engineering

Background: Once formed, tooth enamel and dentin do not undergo remodeling. But dentin that is damaged by injury or disease does undergo limited repair. The reparative dentin is formed by odontoblasts, specialized cells believed to arise from a stem cell population in dental pulp. Until now, no one had ever identified and isolated the precursor cells in adult dental pulp that give rise to odontoblasts.

Advance: Using methodology developed to isolate and characterize bone marrow stem cells, NIH scientists have isolated stem cells from the pulp of adult human teeth and grown them in the laboratory. They transplanted the cells into mice, where they generated a dentin/pulp-like structure. The amount of tissue formed in the transplants far exceeded the amount an individual would normally make during a lifetime. The NIH research demonstrates that adult dental pulp contains cells that are clonogenic, meaning a single cell can give rise to colonies; highly proliferative; and capable of regenerating dental pulp – properties that effectively define them as dental pulp stem cells.

Implications: This study suggests that it may be possible to use adult dental pulp stem cells in tissue engineering. A single tooth could potentially yield enough stem cells to repair dentin in a number of teeth. In the future, researchers may be able to use the stem cell technology to fabricate new teeth to replace those lost through injury or disease.

Grontos S, Mankinim M, Brahim J, Robey PG and Shin S: Postnatal human dental pulp stem cells (DPSCs) i*n vitro and in vivo*. Proceedings of the National Academy of Sciences USA 97: 13625-13630, 2000.

Targeted Drug Delivery to Head and Neck Tumors

Background: Chemotherapy is used for organ preservation, management of recurrent disease, and in combination with radiotherapy in the treatment of head and neck tumors. But since chemotherapy harms healthy cells as well as tumor cells, it produces side effects that sometimes limit the amount of drug that can be given. Antibodies that recognize tumor specific antigens have not been used effectively for drug delivery because they have been unable to penetrate tumor tissue. The use of small peptides that specifically recognize tumor cells may be more effective in targeting drugs to these cells.

Advance: NIH researchers have successfully isolated a 12-amino-acid peptide (HN-1) that meets several criteria for targeted drug delivery into solid tumors. The study showed that the peptide binds to the cancer cells but not adjacent noncancerous tissues. Additionally, HN-1 can be detected both in central portions of the tumors as well as in peripheral tumor cells suggesting that it is able to penetrate the tumor tissue. The study also showed that HN-1 can be internalized by human head and neck squamous cell carcinoma cells and therefore would be capable of transferring drugs across the cell membranes, a critical requirement for drug delivery. Moreover, the peptide localizes to tumors (in mice) when injected into the tail vein, indicating that it would be an effective carrier for an anti-cancer agent when administered intravenously. Interestingly, this peptide appears to be specific for head and neck squamous cell carcinomas.

Implications: These studies establish the potential use of this tumor-specific peptide for targeted drug delivery to head and neck tumors. Specifically, use of this peptide attached to a chemotherapeutic agent may provide the maximally effective dose of a drug to destroy tumors, without producing harmful side effects to other cells.

Hong FD, and Clayman GL: Isolation of a peptide for targeted drug delivery into human head and neck solid tumors. Cancer Research 60: 6551-6556, 2000.

Collaborative Ocular Melanoma Trial

Background: Although it is rare, choroidal melanoma is the most common primary eye cancer in adults. Many choroidal melanomas enlarge over time and lead to loss of vision. Melanoma cells also can spread to other parts of the body and cause death. Because there is no cure for metastatic melanoma, treatment is aimed at keeping the cancer confined to the eye. Enucleation has been the standard treatment for choroidal melanoma for over a century. Interest in radiation therapy emerged twenty years ago as a method to possibly preserve vision and reduce mortality. NIH supported two randomized, controlled clinical trials to follow many patients over a long period of time to compare enucleation versus radiation with respect to survival.

Advance: The results of these studies have revealed that the size of the tumor is the most critical factor in influencing prognosis. Patients with tumors large enough to require removal of the eye were randomized either to receive radiation treatment to the affected eye before it was removed or to having the eye removed without radiation treatment. Patients from both of these groups showed similar five-year survival rates of 60 percent. Patients with medium-sized tumors were randomized either to receive radiation therapy or to have the eye removed. The survival rates were essentially the same in the two groups. Five years after receiving either treatment, 82 percent of the patients were alive. Most patients who received radiation therapy had some vision loss, and some eyes treated with radiation were later removed because of tumor regrowth or other complications.

Implications: As a consequence of this research, the capability of doctors to provide more accurate diagnosis and state-of-the-art treatment for eye cancer has been greatly expanded. With the data showing similar survival rates for radiation therapy versus removal of the eye, quality of life issues become important factors when deciding which of the two treatment options is better for the individual patient.

Hawkins BS: The collaborative ocular melanoma study (COMS) randomized trial of I-125 brachytherapy for choroidal melanoma: III initial mortality findings. COMS Report No.18. Archives of Ophthamology 119: 969-982, 2001.

Protein Involved in Cell Migration in Wound Healing May Inhibit Tumor Growth

Background: The outermost tissue in the visual system is the corneal epithelium. It plays an essential role in preventing pathogens from entering the eye, as well as in providing a barrier to fluid movement into the cornea that would cause swelling and loss of transparency. If the integrity of this epithelium is compromised by trauma, such as mechanical abrasion or chemical burn, the epithelium rapidly is activated to increase cell number (proliferation) and slide over the damaged area (migration) to close the wound and re-establish the barrier function. The corneal epithelium consists of several layers of cells. Immediately after wounding, the most basal cells at the wound margin loosen their attachments to the matrix and to each other. They change shape, and begin sending out processes in order to rapidly close the wound. Proliferation and migration of the epithelium occurs while its integrity as a continuous sheet of cells is maintained. After wound closure is complete, migration ceases and re-attachment occurs. Scientists have identified a number of biochemical components that contribute to the wound healing process. These include growth factors, signaling molecules, cell cycle pathways, cytoskeletal proteins, and cellular adhesion proteins that mediate attachment to other cells as well as the underlying extracellular matrix. Understanding the control of these processes is necessary to enhance the wound healing response in cornea.

Advance: Recently, the cell protein pinin was found in two distinct cellular locations. In the cytoplasm, pinin is associated with desmosomes, structures that mediate cell-to-cell adhesion and serve as attachment points for the intracellular cytoskeleton. This association is lost when cells are migrating in response to wounding but returns after wound closure. Pinin is also found in the cell nucleus. When cells are induced to express pinin, increased cell-to-cell adhesion is observed and inhibition of cell growth and proliferation are observed. Scientists used DNA microarray technology to simultaneously monitor changes in the expression of more than 1200 genes after induction of pinin. They found that only a small number of specific gene subsets are modified by pinin – cell motility genes are stimulated and cell proliferation and migration genes are inhibited.

Implications: Corneal wound healing is a complex process that involves the coordinated response of several regulatory pathways. Closure of a wound by the epithelium requires the intricate coordinated control of cell-to-cell and cell-matrix associations. Identification of the key molecules associated with these structures and the genes that regulate these pathways will lead to treatments that enhance closure and more rapidly restore the epithelial barrier. Since pinin increases cell adhesion and limits migration, it may be possible to enhance wound healing by inhibiting pinin's action. Alternatively, stimulation of pinin expression may play a role in suppression of tumors that develop due to abnormalities in cell adhesion pathways.

Shi Y, Tabesh M, and Sugrue SP: Role of cell adhesion-associated protein, pinin (DRS/memA), in corneal epithelial migration. Investigative Ophthalmology and Visual Science. 41:1337-1345, 2000.

Shi Y., Simmons MN, Seki T, Oh SP, and Sugrue SP: Change in gene expression subsequent to induction of Pnn/DRS/memA: increase in $p21^{cip1/waf1}$. Oncogene 20: 4007-4018, 2001.

Therapy for Retinal Degeneration

Background: Phototransduction is the retinal biochemical process that initiates vision. Light strikes and then activates a molecule of rhodopsin, the visual pigment in rod photoreceptor cells, initiating a cascade of events that ends with visual signals being sent to the brain. Activated rhodopsin is recycled back to its normal inactive state through an enzymatic recovery process involving a molecule of 11-cis retinal, a type of vitamin A. Light accelerates retinal degeneration in several animal model systems, and therefore manipulation of rhodopsin turnover may provide a useful therapeutic strategy for human retinal degenerations in which similar mechanisms of degeneration are involved.

Advance: A derivative of vitamin A called isotretinoin is frequently prescribed in humans for severe acne, but it can impair night vision shortly after such treatment is begun. In a recent research study, isotretinoin was fed to rats to determine whether the night blindness caused by this substance results from the death of rod cells or from some impairment in the ability of the rods to function. The results showed that high doses of isotretinoin caused no observable change in the physical appearance of the rod cells. However, using a sophisticated test of rod function, the electroretinogram, rod cells were seen to have a slow recovery of their physiological function after isotretinoin administration. Biochemical analyses showed decreased levels of 11-cis retinal and the accumulation of abnormal vitamin A derivatives in the treated retinas. This implies that isotretinoin is likely inhibiting the rhodopsin recycling pathway. Interestingly, when isotretinoin was fed to rats carrying an unusual susceptibility to photoreceptor cell damage by light, a protective effect was observed.

Implications: Drug therapies that confer a benefit under certain conditions may have other unknown beneficial or harmful actions. Isotretinoin is useful in treated cases of severe acne, but has the side effect of causing night blindness. Investigations into the cause of this impaired night vision have uncovered a possible strategy for treating retinal and macular degenerations. Isotretinoin reduces the rate at which activated rhodopsin interacts with vitamin A in the phototransduction recovery pathway, but does not cause death of the photoreceptor cells. Therefore, slowing of rhodopsin regeneration by isotretinoin may protect photoreceptors from light damage in certain pathological degenerations.

Sieving PA, Chaudhry P, Kondo M, Provenzano M, Wu D, Carlson TJ, Bush RA, and Thompson DA: Inhibition of the visual cycle in vivo by 13-cis retinoic acid protects from light damage and provides a mechanism for night blindness in isotretinoin therapy. Proceedings of the National Academy of Sciences USA 98: 1835-1840, 2001.

Improving the Effectiveness of a Costly Treatment

Background: Interferon-alpha (IFN-α) is an expensive therapy – and among the very few therapies available – for hepatitis C virus. However, less than 40 percent of patients with hepatitis C respond to this costly treatment. For people with hepatitis C who also are chronic, heavy alcohol drinkers, the scenario is even worse: They are completely unresponsive to IFN-α therapy. Lack of treatments for this group is particularly troubling, because they tend to have much worse liver damage than would be expected from the combination of hepatitis C and alcohol abuse. Their risk of liver cancer increases dramatically. A question that affects a number of research disciplines is why so many hepatitis C patients are resistant to IFN-α therapy and why those with alcoholism are completely unresponsive to it.

A necessary ingredient for liver injury common to both hepatitis C and alcoholic liver disease is an immune-system protein, tumor necrosis factor-alpha (TNF-α). Normally, the inflammation TNF-α produces is therapeutic, but when cells produce it in excess, it damages tissue, including liver tissue. We know that alcohol causes just such damaging, excess production of TNF-α in the liver and that high TNF-α levels correlate strongly with resistance to IFN-α therapy. We also know that proteins associated with the hepatitis C virus stimulate TNF-α receptors – "docking sites" for TNF-α, in cell membranes. This excessive TNF-α receptor activity also contributes to TNF-α-induced damage.

We know, too, that hepatitis C proteins and alcohol not only stimulate TNF-α activity, but also inhibit the series of therapeutic biochemical reactions – the "IFN-α signaling pathway" – that treatment with IFN-α triggers in liver cells. Ultimately, this pathway results in production of antiviral proteins that combat hepatitis C and other viruses. Does TNF-α interfere with the therapeutic IFN-α signaling pathway, thus diminishing the effectiveness of IFN-α treatment? We injected mice with TNF-α to find out.

Advance: In mice, TNF-α suppresses the IFN-α signaling pathway and strongly increases gene activity that produces two proteins in the liver: SOCS3 (suppressor of cytokine signaling 3) and SHP2 (SH2-containing protein-tyrosine phosphatase2). These are the inhibitory proteins that block the effects of IFN-α.

Implications: Altering the activities of SOCS3 and SHP2 could improve the effectiveness of IFN-α treatment for hepatitis C and hepatitis C complicated by alcohol use. About 4 million Americans are infected with hepatitis C, which is easily transmitted and sometimes fatal.

Hong F, Nguyen VA, and Gao B: Tumor necrosis factor α attenuates interferon-α signaling in the liver: involvement of SOCS3 and SHP2 and implication in resistance to interferon therapy. Federation of American Societies for Experimental Biology (in press 2001).

Supplement Given After Birth Prevents Neuro Defects in Mammalian FAS Model

Background: Maternal drinking during pregnancy often results in fetal alcohol syndrome (FAS) and fetal alcohol effects (FAE), which may include debilitating, life-long neurologic and other defects. Their impact on cognition (awareness, knowing, and judgment) and learning – functions of the nervous system – are devastating. These disorders are entirely preventable if women abstain from drinking during pregnancy. However, this best-case scenario is not a realistic one. We need treatments for infants already exposed to alcohol while in the uterus as much as we need effective strategies for preventing pregnant women from drinking in the first place. At present, no such treatments exist.

Supplementing rats' diets with the nutrient choline, part of the B-vitamin complex, before or shortly after birth can lead to long-term improvements in their learning and memory. Choline is a precursor of acetylcholine, one of the chemicals through which nerve cells communicate with each other. It is also a precursor of some of the components of the membrane that surrounds nerve cells, which plays a crucial role in determining what substances can enter and exit cells. Without an intact membrane, nerve cells cannot function properly. The importance of choline in normal development of the nervous system is reflected in the Institute of Medicine's recent recommendations on choline intake for pregnant and lactating women.

Alcohol investigators asked whether giving choline supplements *after* birth also could improve memory and learning in rats that had been exposed to alcohol in their mothers' uteri. The investigators gave rats alcohol throughout pregnancy, then gave their pups either choline or a mild salt-water solution, for comparison, for 3 weeks after birth. Forty-five days after the pups were born, the investigators trained them to perform a visuospatial discrimination task – the pups navigated a maze to reach a light that marked a food reward. Later, the researchers left the light on for only a few seconds, requiring the pups to remember where it was in order to reach their reward.

Advance: Pups that got the salt-water solution after being exposed to alcohol while in the uterus performed much worse on memory and learning tasks than did pups whose mothers had not had any alcohol. Pups that got choline after being exposed to alcohol while in the uterus performed as well as did pups whose mothers had not had alcohol.

Implications: The fact that dietary choline supplements reduced learning and memory impairments even *after* birth has important treatment implications. Some alcohol-induced impairments can be restored to normal, after birth, by early treatment with a nutritional supplement. The beneficial changes that occurred in the rats in this study were long-lasting and may be permanent.

Thomas JD, La Fiette MH, Quinn VRE, and Riley EP: Neonatal choline supplementation ameliorates the effects of prenatal alcohol exposure on a discrimination learning task in rats. Neurotoxicology and Teratology 22: 703-711, 2000.

Widely Used Herbal Remedy, St. John's Wort, Does Not Interfere With Anti-Epileptic Drug

Background: Herbal remedies are widely used by Americans with several billion dollars spent each year. St. John's Wort is a common herbal product often used by the public for the treatment of mild to moderate depression. Since depression is common in patients with seizure disorders, information on possible drug interactions between St. John's Wort and carbamazepine, a commonly used anticonvulsant drug, is important to investigate. A study was undertaken to see if St. John's Wort could be safely used along with carbamazepine, a drug commonly used for treatment of epilepsy and convulsive diseases.

Advance: Researchers at NIH discovered that, in healthy volunteers who have been on carbamazepine for 21 days, use of St. John's Wort for 14 days does not change the blood levels of the anticonvulsant drug. It was concluded that a short course of St John's Wort is not expected to change the pharmacokinetics of the anticonvulsant drug carbamazepine due to enzyme induction.

Implications: Because St. John's Wort is so widely used in the American public, there are ongoing concerns about how the supplement may interfere with prescription drugs. Researchers' findings that short courses of St John's Wort did not change blood levels of carbamazepine in normal volunteers provides additional information regarding use of that herbal agent in patients with convulsive diseases.

Burstein AH, Horton RL, Dunn T, Alfaro RM, Piscitelli SC, and Theodore W: Lack of effect of St. John's Wort on carbamazepine pharmacokinetics in healthy volunteers. Clinical Pharmacology and Therapeutic 68: 605-612, 2000.

Cooking Tumors with Needles: Minimally-invasive, Image Guided Tumor Ablation with Radiofrequency Current

Background: The removal of tumors has traditionally required open surgery with its inherent risks, recovery, and costs. Recent technological developments allow physicians to place a small treatment needle or probe into organs, soft tissue, and solid tumors, and deposit radio wave energy in the tumor and rapidly, safely, effectively, and predictably kill large tumors, without having to surgically remove the tumor. Radiofrequency ablation uses electromagnetic energy to heat tissue in the vicinity of a small needle in a procedure similar to a percutaneous image-guided biopsy.

The factors influencing treatment effects are poorly understood. Blood flow can have a harmful effect by bringing relatively cool body temperature blood into the heated tissue, and limit the effects of the treatment. This has broad treatment implications. The properties of tissue as it is heated are also poorly understood and are being studied in heat-transfer engineering and basic science labs. We are developing methods to harness this heating effect to not only kill tissue, but also to deposit drugs and gene therapy locally. Clinical researchers are investigating the potential applications of this new technology including patients with kidney, liver, and adrenal cancer, as well as painful tumors in patients on sedating pain medications, with no other medical or surgical options. (See http://www.cc.nih.gov/drd/rfa for video of procedure.)

Advance: Kidney cancer has traditionally been approached with open surgical techniques. NIH researchers have applied minimally invasive needle-based treatment systems to this clinical problem in patients with hereditary kidney tumors. Early results suggest that the vast majority of tumors (3 out of 4) can be destroyed with this method in one short treatment session that can be performed on an outpatient basis with minimal risk and a short and uneventful recovery period. Imaging guidance with ultrasound and/or CT scan provides the window into the body that is necessary for such a minimally-invasive procedure. Early results also suggest that this technique can provide lasting pain relief for painful tumors that have not responded to radiation therapy or drugs.

Implications: This technology could have broad medical implications in the liver and kidney, where it is being first applied, as well as economic implications. Tissue can be safely targeted and destroyed in a predictable and safe fashion without the risk and cost of open surgery. The patient with multiple hereditary kidney tumors that appear and grow throughout their lives may benefit from this technique. Current methods of tumor treatment can damage the kidney to the point where dialysis is required three times per week. This technology may provide a simple method of preserving the normal kidney, and avoid kidney failure, without surgery. This patient population also provides a well-controlled model for the treatment of other kidney tumors in patients who may not be surgical candidates. When used to treat painful tumors, this technique can provide the cancer patient with a more alert and less painful quality of life, with less sedating

effects of the usual pain medications. A broad intramural NIH clinical protocol to study this issue is under review.

Wood BJ, and Winkler MT: Radiofrequency thermal ablation as tumor therapy: an overview for the oncology team. Oncology Issues 16: 12-16, 2001.

Pacak K; Fojo T; Goldstein DS; Eisenhofer G; Walther MM; Linehan WM; Bachenheimer L; Abraham J; and Wood B: Radiofrequency ablation: a novel approach for treatment of metastatic pheochromocytoma. Journal of the National Cancer Institute 93: 648-649, 2001.

Long-Acting Antifolate Compared to Shorter-Acting Antifolate for Drug Resistance

Background: Pyrimethamine (PM) plus sulfadoxine (SD) is one of the few remaining affordable drugs for treating uncomplicated malaria in Africa. The combination of the two drugs is also increasingly becoming a first-line treatment for malaria in Africa. Because of the probability that the parasite will acquire drug resistance, the useful therapeutic life of this drug combination is predicted to be around 5 years in sub-Saharan Africa. Understanding the mechanism of antifolate resistance is critical to the rational use of new and available antifolate drugs and to the delay of resistant malaria isolates spreading in Africa. Several theories including uncontrolled drug use and inadequate dosages have attempted to address the reasons for the short effectiveness of this drug combination. The importance of strong selective pressure for therapeutic pyremethanine resistance has rarely been considered.

Advance: In this study, supported through NIH's International Training and Research Program in Emerging Infectious Diseases, researchers from the University of Washington and the Kenyan Medical Research Institute examined whether selection pressure for PM resistance would be minimized if short-acting antifolate drugs were used, despite a longer dosage regimen. Researchers studied specifically the selective pressure exerted by the slowly eliminated combination of PM/SD compared with that of the more rapidly eliminated combination chlorproguanil/dapsone (CPG/Dap) on Kenyan *Plasmodium falciparum.* This parasite is transmitted primarily during the rainy season in tropical areas. After the rainy seasons in Kilifi, a malaria endemic area on the coast of Kenya, there is an increased number of *Anopheles gambiae* mosquitoes followed by an elevated incidence of malaria. Fifty-two children were randomly assigned to three treatment groups: single dosage of PM/SD; single dosage of CPG/Dap; or triple dose of CPG/Dap. Six of the 24 patients in the PM/SD group already had PM resistant parasites before treatment. While only 3 of the 24 participants in the PM/SD group carried triple-mutant parasites before the treatment, there were 9 triple mutant parasites after the treatment. This differed from the mutation rate observed in the CPG/Dap group (2 of 28 before and 5 of 28 after treatment).

Implications: The study demonstrated that the commonly used antifolate PM/SD exerts a stronger selective pressure for resistance than the short-acting antifolate CPG/Dap. Despite the advantage of longer-term eradication of infection from mother and/or newborn (chemoprophylaxis) that PM/SD offers, its higher selective pressure for drug resistant *Plasmodium* strains, which are common in Africa, diminish its effectiveness. The characteristics of the short-acting CPG/Dap suggest it will be a better anti-malarial drug in the longer term, although resistance can also arise with this drug. It is therefore important to consider the co-administration of drugs that have different mechanisms of action, and to change treatment as drugs become ineffective.

Nzila AM, Nduati E, Mberu EK, Sibley CH, Monks SA, Winstanley PA, and Watkins WM: Molecular evidence of greater selective pressure for drug resistance exerted by the long-acting antifolate pyrimethamine/sulfadoxine compared with the shorter-acting chlorproguanil/dapsone on Kenya *plasmodium falciparum*. Journal of Infectious Disease 181: 2023-2028, 2001.

Predictors of Adherence and Plasma HIV Concentrations

Background: A large body of literature indicates that adherence to prescribed medications is generally poor in all patient populations. Compounding low adherence in optimal conditions is the long term nature of drug treatment of many chronic conditions. Treatment of chronic human immunodeficiency disease (HIV) typically requires multiple drugs that must be ingested in a complex schedule more than once a day and in specific relationships to meals and activity. Incomplete adherence to antiretroviral agents can have serious consequences, including loss of plasma HIV suppression and development of drug-resistant HIV strains. This, in turn, can lead to disease progression, inability to suppress HIV even with very intensive regimens and transmission of resistant HIV to others. Other studies have suggested that history of intravenous drug use, use of alcohol and illicit drugs, unstable housing arrangements and various measures of psychiatric disturbance are among factors associated with poor adherence among HIV positive individuals to antiretroviral agents.

Advance: Interviews with HIV positive people on antiretroviral agents revealed that a quarter of the study subjects took fewer than 80 percent of prescribed antiretroviral medications per day over the prior week. Adherence to prescribed complex medication regimens were firmly associated with HIV suppression, to the point that it is reasonable to use adherence as a predictor of HIV load in infected patients. HIV suppression is the major marker of control of HIV disease. This study assisted in identifying individuals at greatest risk of nonadherence, and clearly related adherence to HIV levels in patients' blood. This affirms that focus on adherence by education and patient support is an essential aspect of the treatment plan if adequate control of HIV is to occur.

Implications: Nonadherence to multidrug antiretroviral regimens is worrisome given widespread concerns about drug resistance. The current study successfully linked clinical and psychosocial variables to biologic markers of disease activity. It is clear that there are several modifiable predictors of adherence: self-efficacy, or the confidence in controlling one's behavior, can be improved by providing structured education. Since adherence predicts plasma HIV suppression, efforts should be undertaken to help patients adhere to their medications by helping them better integrate medication regimens into daily routines. In this sample, since African-Americans were independently associated with lower levels of adherence and higher HIV levels, targeted efforts should be developed for that population.

Gifford AL, Bormann JE, Shively MJ, Wright BC, Richman DD, and Bozzette SA: Predictors of self-reported adherence and plasma HIV concentrations in patients on multidrug antiretroviral regimens. Journal of Acquired Immune Deficiency Syndromes 23: 386-395, 2000.

Dementia Family Caregiving Training: Caregiving and Caregiver Outcomes

Background: Managing many chronic diseases, including dementias, relies largely on the ability of family members to master the caregiving role. Family caregivers provide the great majority of home care for persons with dementia and other chronic diseases, and do so for sustained periods of time. They also bear the majority of the costs of care through out-of-pocket expenditures or the direct provision of care. The literature provides ample evidence of additional costs to caregivers: their own mental and physical health, contending with increased stresses in the family, and risk of social isolation. From a policy perspective, support of caregivers is likely to reduce use of health care services (by both caregivers and those receiving care) and delay institutionalization.

The present study implemented the Minnesota Family Workshop designed to provide caregivers with knowledge, skills, and a caregiving outlook so that caregivers can establish their beliefs about caregiving, with the aim of improving scores on depression and other outcomes.

The caregiver/care receiver pairs were randomized either into immediate enrollment in the treatment group, or in a delayed treatment group. The training was provided in weekly, 2-hour sessions over the course of seven weeks. The workshop was structured to reduce adverse stress outcomes of burden and depression.

Advance: The study demonstrates that a short training program focused on important issues relating to the work and role of people who provide care for their community-based relatives with dementia can have positive outcomes for caregivers when measured at three months. Caregivers who completed the workshop, compared to those on the wait-list control group, had better scores on key measures of caregiver outcome: depression, burden, and reaction to their care receiver's problem behaviors. Treatment group caregivers reported feeling less emotionally enmeshed in providing care for their care receivers, and having less of a need to control their care receivers and their behaviors.

Implications: Caregiver health and well being is a major determinant of the decision to institutionalize a relative with dementia. Providing a short term training program can improve the caregivers' ability to provide care to community-resident people with dementia. The policy implications may include delayed institutionalization and reduced health care use by caregivers, as well as improved quality of life for both caregivers and persons receiving care.

Hepburn KW, Tornatore J, Center B, and Ostwald SW: Dementia family caregiver training: affecting beliefs about caregiving and caregiver outcomes. Journal of the American Geriatrics Society 49: 450-457, 2001.

Specialized Home Care Intervention Improves Survival Among Older Post-Surgical Cancer Patients

Background: Cancer is often a disease of older adults, and shortened hospital stays and progressively earlier discharges for many cancer patients have moved the focus of care from hospital to home. Post-surgical patients are discharged with highly complex problems, often accompanied by catheters, dressings, and high technology equipment such as pain medication infusion pumps. Following surgery, patients need monitoring for wound healing, fever, pulmonary complications and pain. In addition, many patients need assistance with ambulation, basic hygiene and meal preparation. The availability and affordability of home care, as well as the health and frailty of caregivers in the family, may have an impact on quality of life of the recovering cancer patient.

A specialized home care intervention was used with 375 post-surgical cancer patients randomized into two groups: one group received usual care and the treatment group received three visits and five telephone calls from advanced practice nurses over a four week period. The nurses assessed and monitored the physical, emotional, and functional status of patients, provided direct care when needed, assisted in obtaining services from the community and provided teaching, counseling, and support to patient and families. The nurses were available 24 hours a day via paging devices.

Advance: Patients receiving the home care intervention at the two-year period following index surgery had a seven month-longer length of survival than the usual care group after adjusting for stage of disease at diagnosis and total length of hospitalization during surgery. The risk of death was approximately doubled among usual care patients compared with those in the intervention group. Neither age, race, depressive symptoms, symptom distress, or enforced social dependency at baseline were predictive of length of survival. Among late-stage patients, the survival advantage at two years is twice those in the usual care group.

The intervention in this study was provided over a longer period of time than usual home health care, was provided by masters'degree-prepared nurses, and included attention to elements of care that may not be a part of usual home health care (symptom control, information about what to expect, psychosocial support and management of surgical complications). The disease progression of cancer can be altered by psychosocial interventions, especially if provided by well prepared health care providers.

Implications: Psychosocial concerns may be assigned a low priority in the face of life and death decisions. Budget pressures mitigate against employment of highly educated (and somewhat highly paid) health care providers. Appropriate intervention provided during the critical time periods of diagnosis and early treatment phases of care influence survival by unknown mechanisms.

McCorkle R, Strumpf NE, Nuamah IF, Adler DC, Cooley ME, Jepson C, and Lusk EJ: A specialized home care intervention improves survival among older post-surgical cancer patients. Journal of the American Geriatrics Society 48: 1707-1713, 2000.

Relaxation and Music Reduces Postsurgical Pain

Background: Surgery now takes place in ambulatory surgical centers or outpatient departments, as well as within hospital operating rooms. Control of post-surgical pain is an increasing problem since discharge from ambulatory surgery or outpatient department surgery is to the home. Once discharged to home, the assessment of pain control is not systematic nor highly professionalized since it is a family member or friend who assesses the pain relief (or over-treatment). After surgery, patients do not always receive sufficient relief from opioid medications (morphine, Demerol, others) and may have undesired side-effects. More complete relief (10 to 30 percent) was found in prior research with combinations of relaxation and music.

The present study compared effects of music and relaxation between days and treatments over a period of time. Random assignment of nearly 500 abdominal surgery patients in five hospitals were made to one of four groups: relaxation, music, their combination, and a control group. Subjects were taught the interventions preoperatively. Since postoperative pain typically increases with ambulation and decreases with rest, in the present study, postoperative testing was at ambulation and rest on days 1 and 2.

Advance: Non-pharmacological methods of pain management are not associated with unpleasant or dangerous side effects of sedation, dizziness or failure to ambulate. In this study, music and relaxation are interventions that are quite inexpensive, can be culturally tailored, and pain was found to decrease by day 2 across ambulation on each day, across ambulation and across rest over both days, and had similar effects by day and by activity. Prior studies have not examined pain management with the interventions of music and relaxation over the postoperative period. The present study amplified information about the mechanism of action of these non-pharmacological interventions in that music was found not only to distract from pain, but also relaxes the individual.

Implications: It is safe to recommend any of these interventions for pain on both postoperative days tested, that is, on day one and day two post-surgery, both at ambulation and at rest. Post-surgical patients can ambulate with greater relief than with patient-controlled analgesia, without increasing opioid intake and incurring possible side-effects.

Good M, Stanton-Hicks M, Grass JA, Anderson GC, Lai HL, Roykulcharoen V, and Adler PA: Relaxation and music to reduce postsurgical pain. Journal of Advanced Nursing 33: 208-215, 2001.

Postoperative Pain Influences Tumor-Promoting Effects of Surgery

Background: Undergoing surgery is well known to result in the suppression of several immune functions including nature killer cell activity (by certain white blood cells) in both animals and humans. Animal studies provide direct evidence of the key role played by natural killer cells in controlling metastasis. Further, there are firm indications that suppression of natural killer cell activity by surgery underlies the promotion of metastatic development that has been historically associated with undergoing surgery.

Taken together, many such studies examining surgery and metastasis suggest that limiting surgery-induced natural killer cell suppression might help reduce metastasis after surgery. Prior research in an animal model found that providing reasonable doses of morphine reduces the tumor-promoting effects of undergoing and recovering from surgery. Considering that many individuals with cancer die of metastatic development, strengthening their resistance to metastatic tumor development is clinically important, especially since surgery is often a necessary first-line strategy for cancer treatment.

Advance: Previous research funded by the NIH was extended in the present study, providing continued support for the view that provision of pain relief reduces surgery-associated increases in the susceptibility to metastasis. The present study adds support to the view that the mechanism of reducing tumor metastasis is pain relief, rather than direct effects on immunity or tumor cells. Interestingly, this is the first study to find that pain alleviation is equally effective for males and females in terms of reducing susceptibility to metastasis.

Implications: Although the present study was conducted in an animal model, it provides evidence that pain relief may be an important aspect of the surgical care of cancer patients. If these relationships can be extended to humans, the study indicates that adequate pain management may protect against metastatic consequences following cancer surgery.

Page GG, Blakeley WP, and Ben-Eliyahu S: Evidence that postoperative pain is a mediator of the tumor-promoting effects of surgery in rats. The Journal of the International Association for the Study of Pain 90: 191-199, 2001.

Uncoupling Proteins: A New Way to Burn Fat?

Background: Obesity can lead to development of type 2 diabetes, and the incidence of both diseases is increasing in the U.S. Clinical studies have demonstrated that diet and exercise are effective treatments for both obesity and type 2 diabetes. However, many individuals are unable to adhere to these types of treatment programs or find them only minimally effective. Consequently, scientists continue to search for ways to develop drugs that help people burn excess calories and prevent weight gain, thus reducing the incidence of obesity and type 2 diabetes.

Advance: Scientists have identified a family of proteins, termed uncoupling proteins, that are localized to the mitochondria within cells. Just as an automobile uses the energy released by burning fuel to propel the drive shaft, mitochondria convert nutrients, like glucose and fatty acids, into energy used to perform all of the necessary functions of living cells. Some of the energy generated by burning gasoline is given off as heat, and cars are equipped with an elaborate cooling system to dissipate excess heat. Mitochondria also generate heat as they burn nutrients, and this is used to maintain the body's temperature. If more calories are consumed than are necessary to maintain bodily functions and body temperature, these calories are stored as fat. Uncoupling proteins, first identified in rodents, steal some of the energy produced by burning nutrient fuel, and convert it to heat, which allows many animal species to survive cold winters without food. Knowing how these proteins work may allow scientists to develop new drugs that would redirect excess calories as dissipated heat rather than as stored fat. One uncoupling protein, uncoupling protein 2, is expressed in the beta cells of the pancreas as well as in muscle and fat cells. Pancreatic beta cells secrete insulin to regulate blood sugar levels, and beta cell malfunction leads to diabetes. Ongoing investigations suggest that the amount of uncoupling protein in the beta cells plays a crucial role in regulating insulin production in response to blood sugar. Thus, insufficient levels of uncoupling protein 2 could contribute to diabetes, where blood sugar is uncontrolled. Another group of investigators demonstrated that mice engineered to over-express a fat cell uncoupling protein in their muscle cells weighed less than other mice fed the same amount of food and were resistant to obesity even when fed high-fat diets. Expression of uncoupling protein in muscle also prevented the cells from becoming resistant to insulin, thus preventing the mice from becoming diabetic. A third group of investigators found evidence that common variations in the uncoupling protein 2 gene may be responsible for the differences in human susceptibility to weight gain. Although these studies reached different conclusions about the role and/or critical amount of uncoupling protein in different cell types, they all substantiate the idea that strict regulation of uncoupling proteins is vital and that mis-regulation could result in obesity and diabetes.

Implications: Because these studies suggest that uncoupling proteins are involved in energy and blood sugar regulation, uncoupling proteins may be important targets for new drug development. Once the critical role and regulatory mechanism of the various uncoupling proteins have been established, scientists can search for drugs to manipulate levels of these proteins in order to prevent or control both obesity and diabetes.

Li B, Nolte LA, Ju JS, Han DH, Coleman T, Holloszy JO, and Semenkovich CF: Skeletal muscle respiratory uncoupling prevents diet-induced obesity and insulin resistance in mice. Nature Medicine 6: 1115-1120, 2000.

Zhang CY, Baffy G, Perret P, Krauss S, Peroni O, Grujic D, Hagen T, Vidal-Puig AJ, Boss O, Kim YB, Zheng XX, Wheeler MB, Shulman GI, Chan CB, and Lowell BB: Uncoupling protein-2 negatively regulates insulin secretion and is a major link between obesity, β cell dysfunction, and type 2 diabetes. Cell 105: 745-755, 2001.

Alternatives to Pancreatic Islets: Stem Cells and Bioengineering

Background: Type 1 diabetes is a disease in which the immune system destroys insulin-producing beta cells within the pancreas. People with type 1 diabetes require lifelong insulin replacement to control their blood sugar and would not survive without such treatment. However, current methods of insulin replacement are not a cure for type 1 diabetes. Individuals suffering from diabetes remain susceptible to many debilitating complications of the disease that arise from the inability to tightly regulate blood sugar levels. Recently, a new treatment in which human pancreatic islets procured from organ donors are transplanted into a patient with diabetes has shown promise as a means of treating this disease. Several patients receiving this treatment have been able to remain free of the burden of daily insulin injections for more than a year. Because of the limited supply of donor organs for this procedure, scientists are exploring other means to generate insulin-producing cells with the hope of making lifesaving islet transplantation more widely available.

Advance: Two studies have demonstrated promise with very different approaches to cell-based insulin replacement therapy. Certain cells, called stem cells, have the potential to grow and divide indefinitely in an undifferentiated state. Early embryos contain many such cells, which, when prompted with the right signal, can then begin to develop characteristics and specialized functions that define all of the organs and tissues of the body. These cells are known as stem cells. In certain tissues, stem cells appear to exist even in the adult, for example in bone marrow, thus providing a continuing source of renewal for blood cells. Scientists have postulated that stem cells might provide a replenishable source for cells to treat a number of diseases, including diabetes. One group has suggested that such cells may even exist in the adult pancreas. They have reported that treatment with certain trophic (nutrition) factors can double the number of islet cells and have used this model to try to identify islet stem cells. They looked for these cells by looking for the presence of a protein, nestin, that has been identified as a marker for potential neural stem cells. They found a population of cells in both human and rat adult pancreas that expressed nestin, but did not express other proteins associated with more mature differentiated cells of the endocrine or exocrine pancreas. These cells appear to have the ability to grow and divide as well as to differentiate in culture into all of the cell types of the pancreas and surprisingly, can even develop into liver cells. Such cells could potentially be transplanted into diabetic patients if scientists can learn how to isolate them in sufficient numbers and control their differentiation into pancreatic islet cells.

A complementary strategy to restore insulin production would be to engineer cells to act as replacement beta cells. Such cells would not only have to produce and secrete insulin, but they would have to be able to respond to blood glucose levels with the same degree of precision as a natural beta cell. The cells of the intestine are an attractive target because they are numerous and easily accessible. Scientists generated mice carrying the human insulin gene within their DNA. To direct cells in the intestine to produce insulin, they combined the insulin gene with the regulatory elements from a gene normally found in specific intestinal cells, K cells. They carefully selected a gene which was already known to be regulated by glucose in a pattern very

similar to insulin. The resulting mice possess K cells that not only secrete insulin but whose insulin production changes with blood glucose levels. To test their hypothesis that such an approach could be used to treat type 1 diabetes, they treated the animals with a drug that destroyed the animals' beta cells. Normally, animals who received this treatment develop diabetes and die in a few days unless they receive insulin injections. However, animals with the genetically engineered insulin-producing cells in their intestine not only survived, but had blood glucose levels indistinguishable from normal animals even if given a glucose challenge. This indicates that the K cells produced sufficient insulin in a pattern that paralleled the normal pancreatic islet.

Implications: The identification of a population of stem cells within pancreatic islets could provide a source of insulin for people whose beta cells have been destroyed as a result of type 1 diabetes. It may also be possible to use other cells as surrogate insulin producers to maintain normal blood sugar levels, even in the absence of pancreatic islet-derived insulin. While both results are preliminary, they point to promising areas of research which may indeed lead to a cure for type 1 diabetes.

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Safe and Effective Therapy for Fabry Disease

Background: Fabry disease is a rare genetic disorder caused by a deficiency of the enzyme, α-galactosidase A. Because the gene is located on the X chromosome, mostly males are affected, although female carriers of the defective gene may exhibit symptoms of the disease. The disease affects an estimated 2,000 to 4,000 males in the U.S. The enzyme normally helps to break down a fat (or lipid) called globotriaosylceramide, or GL-3. Without adequate α-galactosidase A, GL-3 accumulates in the cells, tissues, and organs of affected patients. Over time, this buildup of GL-3 causes damage to the heart, kidneys, and brain, leading to life-threatening problems. The earliest symptoms of Fabry disease usually appear during childhood or adolescence and include severe nerve pain causing burning sensations in the hands and feet. As they grow older, individuals may have impaired circulation leading to early heart attacks, strokes, and many other medical problems. The kidneys become progressively involved resulting in a need for dialysis or kidney transplantation. Treatment has been limited to symptomatic management of pain and the end-stage complications of kidney disease, heart disease, and stroke.

Advance: This year, investigators demonstrated the feasibility of enzyme replacement to correct the metabolic defect in Fabry disease. Proof of concept studies were published in a mouse model of the disease and a phase 1 dose escalation study was performed to demonstrate safety. Two double-blind clinical trials were published, one was conducted at the NIH Clinical Center and the other by the International Collaborative Fabry Disease Study Group. In the latter study, patients were randomly assigned to receive recombinant α-galactosidase A or a placebo. Patients received 11 infusions of recombinant α-galactosidase A over a 20 week period. Heart, kidney, and skin biopsies were examined for deposits of GL-3 both before and during treatment. Investigators were primarily concerned with the levels in the kidney since kidney failure is a major feature of Fabry disease. Approximately 69 percent of the 29 patients had a return to near normal levels of GL-3 in their kidneys, with the remainder showing significantly decreased levels. The skin and heart were also markedly improved. Following the initial 20 weeks, the study was extended into an open-label design. This extended study confirmed the results of the double-blind study and showed that the heart, kidneys, and skin remained clear of deposits or that deposits were further reduced over the treatment period. In addition, patients reported improvement in their pain and in quality-of-life. All of the patients elected to continue the treatment after the trial was completed.

Implications: Fabry disease is one of a group of over 40 diseases collectively known as lysosomal storage disorders, which includes Tay Sachs, Niemann Pick, and Gaucher disease. Like Gaucher disease, the manifestations are mainly in the periphery where enzyme replacement can eliminate the harmful buildup of GL-3, thereby reducing the complications of the disease and improving quality-of-life. Fabry disease now joins Gaucher disease as a treatable lysosomal storage disorder.

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Benefits of Antiretroviral Therapy in HIV-positive Children

Background: Despite dramatic gains in reducing mother-to-child transmission of HIV, approximately 20,000 children, including adolescents, are living with HIV infection in the U.S. Both survival time and quality of life have improved dramatically in HIV-positive children with the introduction of highly active antiretroviral therapy (HAART), a potent combination of drugs that includes an HIV protease inhibitor (PI). The growth patterns in children prior to the introduction of HAART indicate that HIV-positive children have similar birth weights compared with non-infected children but that they fall behind in both weight and height within the first months of life. The current study was designed to determine whether HAART therapy could have a positive impact on these and other growth parameters in HIV-infected children.

Advance: Researchers monitored the growth of 67 HIV-positive children who were treated with HAART including one PI. The children were followed for over two years, during which time they received the PI for approximately five months total. After two and one-half years, treatment with PIs resulted in significant increases in weight, weight-for-height, and arm muscle circumference compared to their status prior to PI therapy. A smaller effect was seen on height alone. PI therapy also reduced levels of HIV in the children's blood by nearly 80 percent.

Implications: The use of PIs in the treatment of children with HIV infection has a beneficial effect, resulting in improvement of several growth parameters. Adult HIV-positive patients receiving HAART sometimes develop complications, specifically a potentially serious metabolic syndrome that results in redistribution of body fat, abnormal lipids, and insulin resistance or diabetes. Whether such complications may also appear in children will be a topic of future studies.

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Increased Risk of Cardiovascular Disease in HIV-Positive Patients with Fat Redistribution Associated with Antiretroviral Therapy

Background: Current therapy for HIV usually involves a multi-drug regimen known as highly active antiretroviral therapy (HAART). Prolonged HAART is associated with a potentially serious metabolic syndrome that may result in fat redistribution, lipid abnormalities, and insulin resistance or diabetes. Many of these metabolic changes are known to be associated with increased risk of cardiovascular disease in patients without HIV infection. However, the cardiovascular risk in HIV-infected patients with this metabolic syndrome is unknown. Elevated levels of a number of circulating enzymes, including plasminogen activator inhibitor-1 (PAI-1) and tissue-type plasminogen activator (tPA), are risk factors for cardiovascular diseases, heart attacks, and strokes.

Advance: Scientists studied 86 patients with HIV infection who were receiving HAART and had had recent changes in body fat distribution. Thirty three of these patients were found to have impaired glucose tolerance or hyperinsulinemia, two risk factors for type 2 diabetes. These patients also had elevated levels of PAI-1 and tPA, suggesting that they were at elevated risk for cardiovascular disease. A subset of these individuals were then enrolled in a study designed to determine whether the drug metformin, used in the treatment of type 2 diabetes, could be beneficial to HIV-infected people with metabolic complications of HAART. After three months, patients who received metformin demonstrated significant improvements in their hyperinsulinemia as well as reductions in the levels of PAI-1 and tPA.

Implications: HIV-infected individuals who develop metabolic changes on HAART may display elevated levels of circulating PAI-1 and tPA, two early markers of impaired fibrinolysis and risk factors for cardiovascular events. The improvement seen in these parameters in HIV-positive patients following metformin therapy mirrors a result seen in the treatment of HIV-negative diabetic patients. This result suggests that metformin may lower the cardiovascular disease risk in HIV-infected patients who develop metabolic complications of HAART.

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Urinary Tract Infection: Recurrence, Anti-microbial Resistance, and Self-treatment

Background: Urinary tract infections (UTIs) are among the most common infectious diseases acquired by humans – only respiratory infections occur more often. Women are especially prone to UTIs. The current drug of choice for treatment of uncomplicated UTIs is trimethoprim-sulfamethoxazole (TMP-SMX), though many other antibiotics are used. However, antibiotic-resistant UTIs are increasing.

Advance: Often, young women have UTIs but do not have symptoms of the infection. A recent study demonstrated that bacteria in the urine without symptoms is common and rarely persists. It is, however, a strong predictor of subsequent symptomatic UTI.

A second study showed that empirical treatment of UTIs with TMP-SMX, before the results of microbiological tests are known, leads to lower cure rates when the infecting organism is resistant to this drug.

A third study showed that women who had a history of recurrent UTIs could accurately diagnose, self-treat, and cure their infections. In this uncontrolled study of 172 women in a university-based primary health care clinic, 88 women self-diagnosed 172 UTIs, which were confirmed by laboratory evaluation. The women subsequently self-treated with ofloxacin or levofloxacin. The cure rate exceeded 90 percent.

Implications: These studies make a substantial contribution to clinical decision making for a very common office problem faced by primary care physicians. They establish in a large population based study that bacteria in the urine do not automatically lead to infection. Self-treatment of uncomplicated recurrent UTIs with ofloxacin or levofloxacin is very effective in curing infection. At the same time, resistance to commonly used drugs can be problematic. While on the one hand, self-diagnosis followed by self-treatment simplifies the care of women with recurrent UTIs, physicians should use a management strategy that considers bacterial resistance and other factors (such as adverse effects and cost-effectiveness) so that the most effective drugs are used.

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Analysis Suggests that Previous Kidney Dialysis Shortens Survival of Subsequent Kidney Transplant Grafts

Background: Many studies have been conducted to determine the relative benefits of kidney transplantation versus dialysis for patients with end-stage kidney failure. Research shows that patients who receive kidney transplants survive longer than similar patients who undergo long-term dialysis. Whether kidney dialysis affects subsequent kidney transplant graft survival is controversial. Approximately one-fourth of kidney transplants in the U.S. are performed in adult recipients who have not had long-term dialysis.

Advance: Researchers found that survival of kidneys transplanted in recipients who had a transplant early in the progression of renal disease, prior to needing dialysis, was superior compared with kidneys transplanted in patients who had been on long-term dialysis. The graft failure rate was reduced 52 percent after one year, 82 percent after two years, and 86 percent over subsequent years. Using data from the U.S. Renal Data System (USRDS), investigators studied over 8,000 patients who either were or were not treated by long-term dialysis before receiving a kidney transplant from a living donor. Adjustments to the data were made for confounding variables, including the transplantation center and median household income.

Implications: This analysis suggests that it might be better for a patient with end-stage kidney failure to receive a kidney transplant before long-term dialysis is initiated, a finding of substantial importance for care of the patient with failing kidneys. However, this observation needs to be confirmed by other studies to assure that it is not a consequence of differences in the patient groups that elect the two kinds of therapy.

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